

**CSR  
Clinical  
Projects  
and  
Cores**

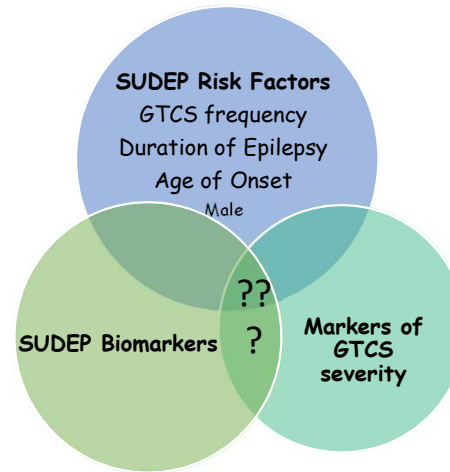
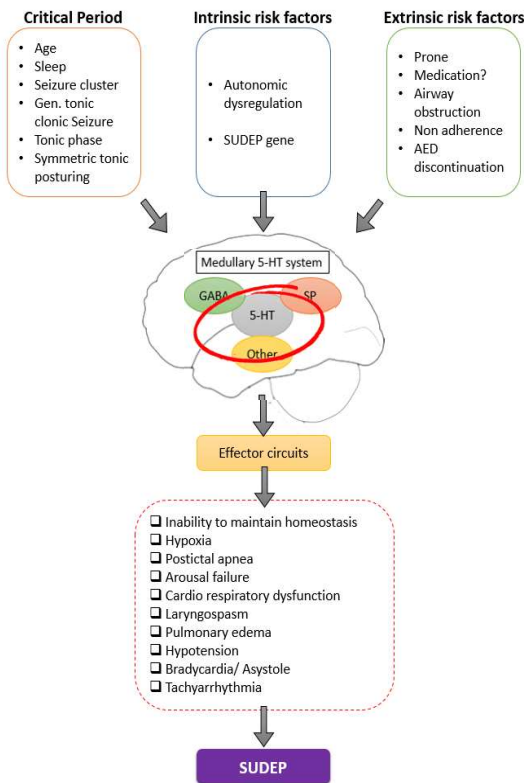
**Sam Lhatoo  
MD FRCP**

# Key Areas of Focus

- Characterization of cardiac and respiratory dysfunction in epileptic seizures
- Identification of cardiorespiratory control/modulation sites in the brain
- Identification of clinical biomarkers of SUDEP risk
- Identification of imaging biomarkers of SUDEP risk
- Creation of a large, multimodal, prospective database of high-risk, near-SUDEP and SUDEP patients as an open resource for SUDEP researchers
- Mentorship of a new generation of SUDEP researchers

# SUDEP, Convulsive Seizure Severity and their Biomarkers

## SUDEP Pathomechanisms



## Proposed Biomarkers of SUDEP And Markers of GTCS Severity

- Prolonged post-ictal EEG suppression  
*Ryvlin 2013, Lhatoo 2010*
- Prolonged tonic phase of the GTCS  
*Tao 2013*
- Decerebration during the tonic phase  
*Alexandre 2015*
- Peri-ictal central apnea/hypoxia  
*Nashef 1996, So 2000, Schuele 2000, Jin 2017*
- Peri-ictal peripheral apnea/hypoxia  
*Tavee 2008, Stewart 2017*
- Post-ictal bradycardia/asystole  
*Ryvlin 2013, Nashef 1996*
- Peri-ictal tachyarrhythmia  
*Ryvlin 2013, Ferlisi 2013, Jin 2017*
- Peri-ictal hypotension/baroreflex failure  
*Bozorgi 2013, Hampel 2017*
- Arousal failure/post-ictal immobility  
*Kuo 2016, Seyal 2013*

# Peri-ictal cardio-respiratory dysfunction

## a) Ictal Central apnea

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

### The incidence and significance of periictal apnea in epileptic seizures

Nuria Lacuey<sup>1</sup> | Bilal Zonjy<sup>2</sup> | Johnson P. Hampson<sup>1</sup> | M. R. Sandhya Rani<sup>2</sup> | Anita Zaremba<sup>2</sup> | Rup K. Sainju<sup>2,3</sup> | Brian K. Gehlbach<sup>2,3</sup> | Stephan Schuele<sup>2,4</sup> | Daniel Friedman<sup>2,5</sup> | Orrin Devinsky<sup>2,5</sup> | Maromi Ne<sup>2,6</sup> | Ronald M. Harper<sup>2,7</sup> | Luke Allen<sup>2,8</sup> | Beate Diehl<sup>2,8</sup> | John J. Millichap<sup>2,9</sup> | Lisa Bateman<sup>2,10</sup> | Mark A. Granner<sup>2</sup> | Deidre N. Dragon<sup>2</sup> | George B. Richerson<sup>2,3</sup> | Samden D. Lhatoo<sup>1,2</sup>

<sup>1</sup>Epilepsy Center, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

<sup>2</sup>NINDS Center for SUDEP Research (CSR), Cleveland, OH, USA

<sup>3</sup>University of Iowa School of Medicine, Iowa City, IA, USA

<sup>4</sup>Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

<sup>5</sup>NYU Langone School of Medicine, New York, NY, USA

<sup>6</sup>Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA

<sup>7</sup>Department of Neurobiology and the Brain Research Institute, University of California, Los Angeles (UCLA), Los Angeles, CA, USA

<sup>8</sup>Institute of Neurology, University College London, London, UK

<sup>9</sup>Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

<sup>10</sup>Department of Neurology, Columbia University, New York, NY, USA

#### Correspondence

Nuria Lacuey, Epilepsy Center, University Hospitals Cleveland Medical Center, Cleveland, OH, USA.  
Email: nuria.lacuey@uhospitals.org

#### Funding information

Center for SUDEP Research; NIH/NINDS Grant/Award Number: U01-NS090405 U01-NS090407 U01-NS090415

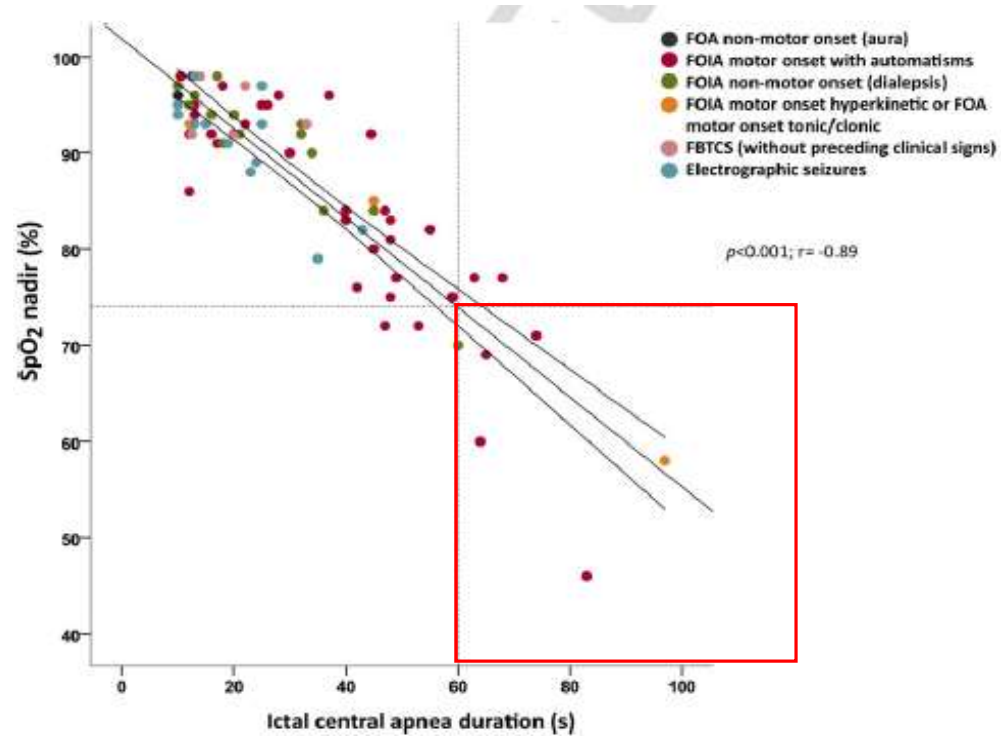
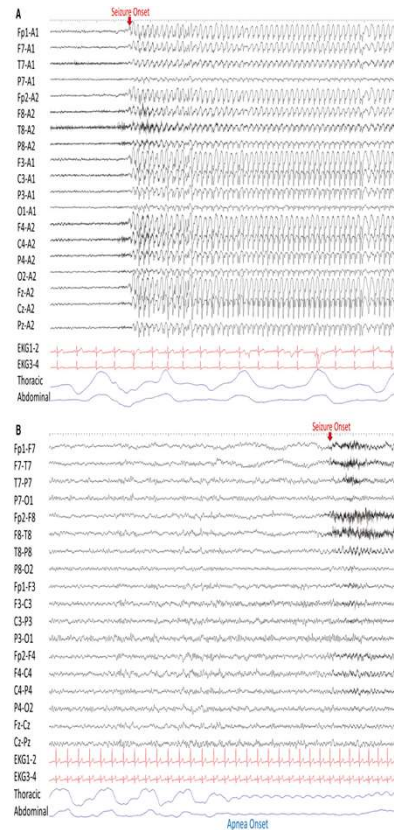
#### Summary

**Objective:** The aim of this study was to investigate periictal central apnea as a seizure semiological feature, its localizing value, and possible relationship with sudden unexpected death in epilepsy (SUDEP) pathomechanisms.

**Methods:** We prospectively studied polygraphic physiological responses, including inductance plethysmography, peripheral capillary oxygen saturation (SpO<sub>2</sub>), electrocardiography, and video electroencephalography (VEEG) in 473 patients in a multicenter study of SUDEP. Seizures were classified according to the International League Against Epilepsy (ILAE) 2017 seizure classification based on the most prominent clinical signs during VEEG. The putative epileptogenic zone was defined based on clinical history, seizure semiology, neuroimaging, and EEG.

**Results:** Complete datasets were available in 126 patients in 312 seizures. Ictal central apnea (ICA) occurred exclusively in focal epilepsy (51/109 patients [47%] and 103/312 seizures [36.5%]) ( $P < .001$ ). ICA was the only clinical manifestation in 16/103 (16.5%) seizures, and preceded EEG seizure onset by  $8 \pm 4.9$  s, in 56/103 (54.3%) seizures. ICA  $\geq 60$  s was associated with severe hypoxemia (SpO<sub>2</sub> <75%). Focal onset impaired awareness (FOIA) motor onset with automatisms and FOIA nonmotor onset semiologies were associated with ICA presence ( $P < .001$ ), ICA duration ( $P = .002$ ), and moderate/severe hypoxemia ( $P = .04$ ). Temporal lobe epilepsy was highly associated with ICA in comparison to extratemporal epilepsy ( $P = .001$ ) and frontal lobe epilepsy ( $P = .001$ ). Isolated postictal central apnea was not seen; in 3/103 seizures (3%), ICA persisted into the postictal period.

**Significance:** ICA is a frequent, self-limiting semiological feature of focal epilepsy, often starting before surface EEG onset, and may be the only clinical manifestation of focal seizures. However, prolonged ICA ( $\geq 60$  s) is associated with severe hypoxemia and may be a potential SUDEP biomarker. ICA is more frequently seen in temporal than extratemporal seizures, and in typical temporal seizure semiologies. ICA rarely persists after seizure end. ICA agnosia is typical.



# Peri-ictal cardio-respiratory dysfunction

## b) Post-convulsive central apnea ± bradycardia

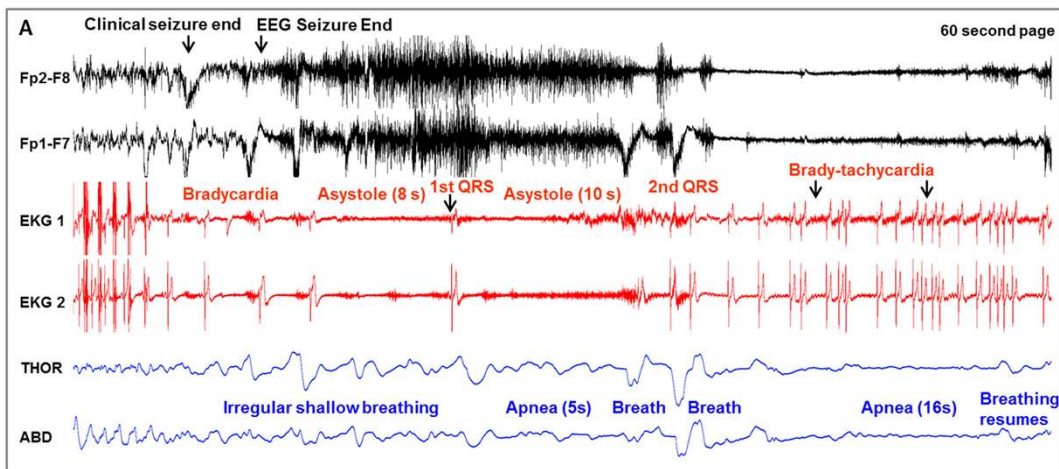
ARTICLE

### Postconvulsive central apnea as a biomarker for sudden unexpected death in epilepsy (SUDEP)

Laura Vilella, MD, Nuria Lacuey, MD, Johnson P. Hampson, MSBME, M.R. Sandhya Rani, PhD, Rup K. Sainju, MBBS, Daniel Friedman, MD, Maromi Nel, MD, Kingman Strohl, MD, Catherine Scott, MPHIL, Brian K. Gehlbach, MD, Bilal Zonjy, MD, Norma J. Hupp, Anita Zaremba, BA, Nassim Shafiqabadi, MD, Xiuhe Zhao, MD, Victoria Reick-Mitrisin, MS, Stephan Schuele, MD, MPH, Jennifer Ogren, PhD, Ronald M. Harper, PhD, Beate Diehl, MD, PhD, FRCP, Lisa Bateman, MD, Orrin Devinsky, MD, George B. Richerson, MD, PhD, Philippe Ryvlin, MD, PhD, and Samden D. Lhatoo, MD, FRCP

**Correspondence**  
Dr. Vilella  
lvilella@stanford.edu

Neurology® 2019;92:e171-e182. doi:10.1212/WNL.0000000000006785



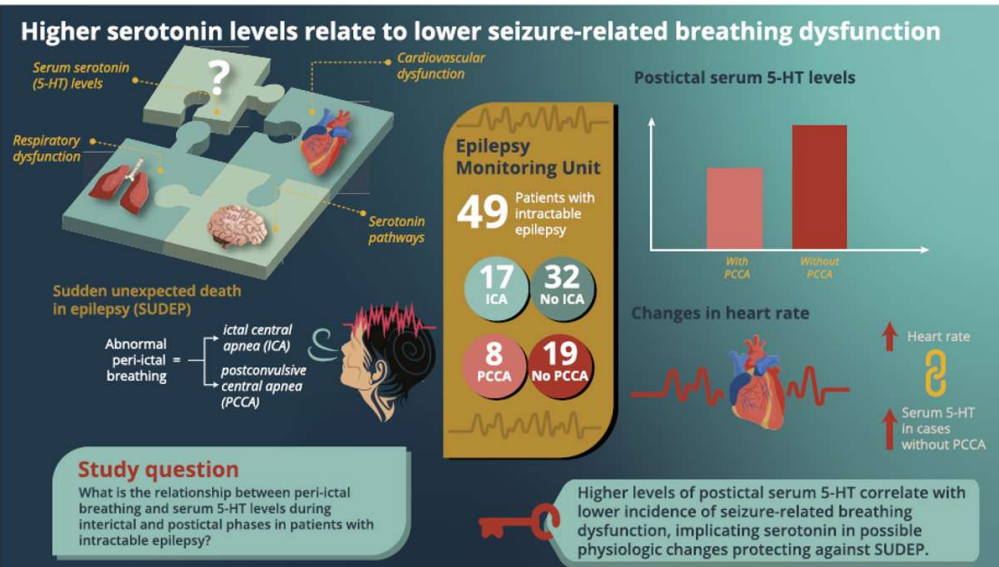
ARTICLE

### Postictal serotonin levels are associated with peri-ictal apnea

Arun Murugesan, BA, M.R. Sandhya Rani, PhD, Laura Vilella, MD, Nuria Lacuey, MD, PhD, Johnson P. Hampson, MS, Carl L. Faingold, PhD, Daniel Friedman, MD, Orrin Devinsky, MD, Rup K. Sainju, MBBS, Stephan Schuele, MD, MPH, Beate Diehl, MD, PhD, FRCP, Maromi Nel, Ronald M. Harper, PhD, Lisa M. Bateman, MD, George Richerson, MD, PhD, and Samden D. Lhatoo, MD, FRCP

**Correspondence**  
Dr. Rani  
M.R.Sandhya.Rani@stanford.edu

Neurology® 2019;93:1-10. doi:10.1212/WNL.0000000000008244



# Peri-ictal cardio-respiratory dysfunction

## c) Functional evidence of brainstem compromise

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

### Ventilatory response to CO<sub>2</sub> in patients with epilepsy

Rup K. Sainju<sup>1</sup> | Deidre N. Dragon<sup>1</sup> | Harold B. Winnike<sup>2</sup> | Marcus B. Nashelsky<sup>3</sup> | Mark A. Granner<sup>1</sup> | Brian K. Gehlbach<sup>1,4</sup> | George B. Richerson<sup>1,5,6</sup>

<sup>1</sup>Department of Neurology, University of Iowa Carver College of Medicine, Iowa City, Iowa  
<sup>2</sup>Institute for Clinical and Translational Science, University of Iowa Carver College of Medicine, Iowa City, Iowa  
<sup>3</sup>Department of Pathology, University of Iowa Carver College of Medicine, Iowa City, Iowa  
<sup>4</sup>Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, Iowa  
<sup>5</sup>Department of Molecular Physiology and Biophysics, University of Iowa Carver College of Medicine, Iowa City, Iowa  
<sup>6</sup>Veterans Affairs Medical Center, Iowa City, Iowa

**Correspondence**  
 Rup K. Sainju, Department of Neurology, University of Iowa Carver College of Medicine, 200 Hawkins Drive, RCP-Neurology Clinic, Iowa City, IA.  
 Email: rup-sainju@uiowa.edu

**Funding information**  
 This study was supported by the National Institute of Neurological Disorders and Stroke: U01 NS090414 (Center for SUDEP Research), Citizens United for Research in Epilepsy (CURE)—SUDEP award, and National Institute of Health CISA program grant U54TR001356. The Sentec Digital Monitoring System was provided by the company. The company was not involved in the design, execution, analysis, or reporting of this study.

#### Summary

**Objectives:** Severe peri-ictal respiratory depression is thought to be linked to risk of sudden unexpected death in epilepsy (SUDEP) but its determinants are largely unknown. Interindividual differences in the interictal ventilatory response to CO<sub>2</sub> (hypercapnic ventilatory response [HCVR] or central respiratory CO<sub>2</sub> chemosensitivity) may identify patients who are at increased risk for severe peri-ictal hypoventilation. HCVR has not been studied previously in patients with epilepsy; therefore we evaluated a method to measure it at bedside in an epilepsy monitoring unit (EMU) and examined its relationship to postictal hypercapnia following generalized convulsive seizures (GCS).

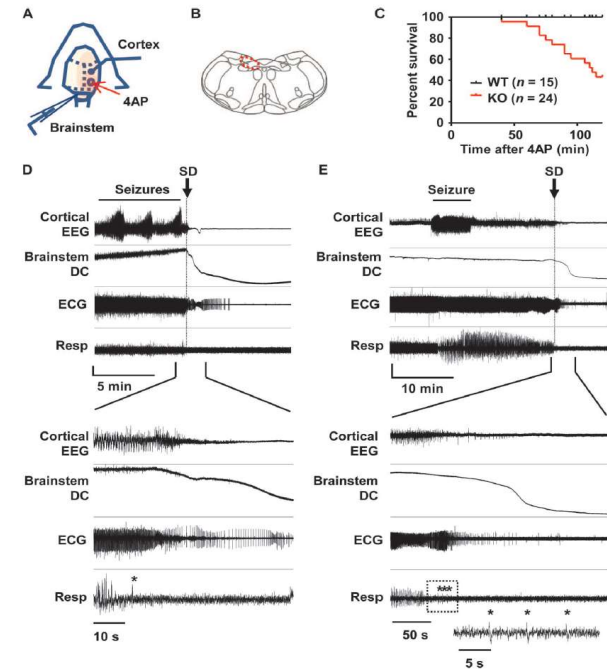
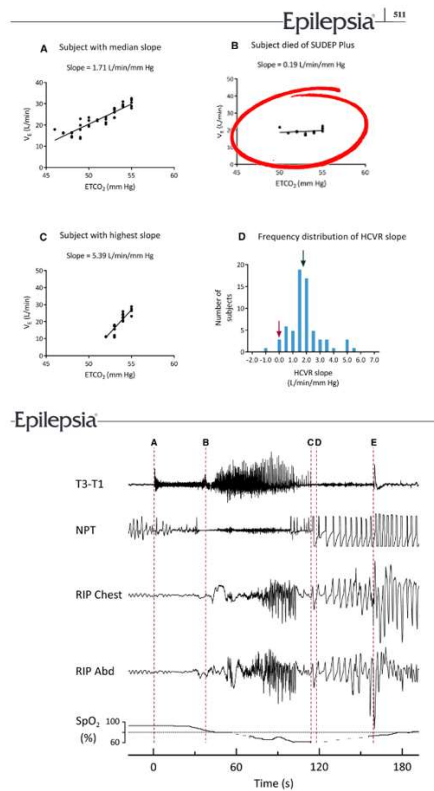
**Methods:** Interictal HCVR was measured by a respiratory gas analyzer using a modified rebreathing technique. Minute ventilation (V<sub>E</sub>), tidal volume, respiratory rate, end tidal (ET) CO<sub>2</sub> and O<sub>2</sub> were recorded continuously. Dyspnea during the test was assessed using a validated scale. The HCVR slope ( $\Delta V_E / \Delta ET CO_2$ ) for each subject was determined by linear regression. During the video-electroencephalography (EEG) study, subjects underwent continuous respiratory monitoring, including measurement of chest and abdominal movement, oronasal airflow, transcutaneous (tc) CO<sub>2</sub> and capillary oxygen saturation (SpO<sub>2</sub>).

**Results:** Sixty-eight subjects completed HCVR testing in 151 ± (standard deviation) 58 seconds, without any serious adverse events. HCVR slope ranged from -0.94 to 5.39 (median 1.71) L/min/mm Hg. HCVR slope correlated with the degree of unpleasantness and intensity of dyspnea and was inversely related to baseline ET CO<sub>2</sub>. Both the duration and magnitude of postictal tcCO<sub>2</sub> rise following GCSs were inversely correlated with HCVR slope.

**Significance:** Measurement of the HCVR is well tolerated and can be performed rapidly and safely at the bedside in the EMU. A subset of individuals has a very low sensitivity to CO<sub>2</sub>, and this group is more likely to have a prolonged increase in postictal CO<sub>2</sub> after GCS. Low interictal HCVR may increase the risk of severe respiratory depression and SUDEP after GCS and warrants further study.

#### KEYWORDS

biomarker, central chemoreponsiveness, epilepsy, generalized convulsive seizures, hypercapnia, SUDEP



**Fig. 1.** Premorbid cardiorespiratory dysregulation and brainstem SD in Kv1.1 mutant associated with cortical seizures in vivo. (A) Diagram of experimental setup for application of 4AP and recording of EEG and brainstem DC potentials in spontaneously breathing urethane-anesthetized juvenile mice (P18 to P25). (B) Illustration of brainstem recording area (red circle). (C) Time until death in Kv1.1 wild-type (WT) and KO mice after focal 4AP application. (D and E) Representative traces of premonitory sequence of the cortical EEG, brainstem DC current, ECG, and respiration in two Kv1.1 KO mice. Expanded traces shown in the lower half of the panels illustrate the temporal association between loss of cortical EEG activity, brainstem SD, and development of cardiorespiratory arrhythmias. Asterisk, gasping. (D) Immediate postictal EEG flattening tightly coupled to onset of cardiorespiratory dysregulation and brainstem SD. Vertical scale: cortical EEG, 0.35 mV; brainstem DC, 5 mV; ECG, 0.22 mV; respiration, arbitrary units. (E) Delayed cortical suppression and cardiorespiratory shutdown >10 min after final intense seizure activity. The respiratory trace in the box is further expanded and shown in the inset. Vertical scale: cortical EEG, 0.31 mV; brainstem DC, 18 mV; ECG, 0.43 mV; respiration, arbitrary units.

# Peri-ictal cardio-respiratory dysfunction

## d) Structural evidence of brainstem compromise

### RESEARCH ARTICLE

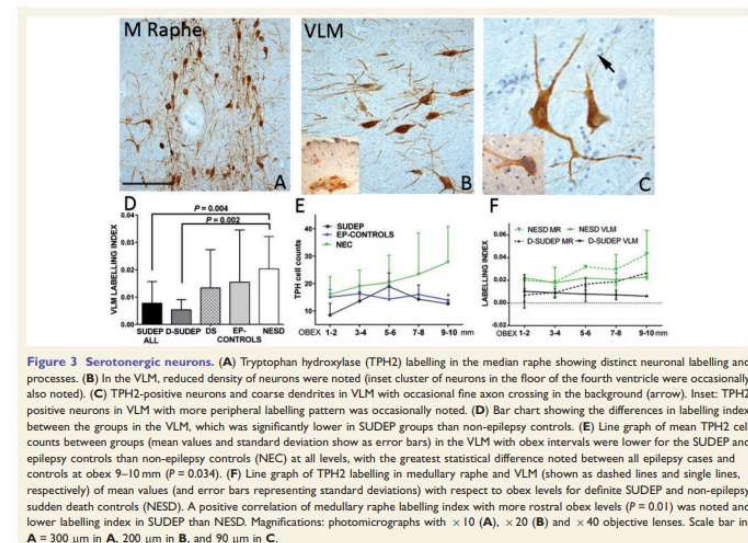
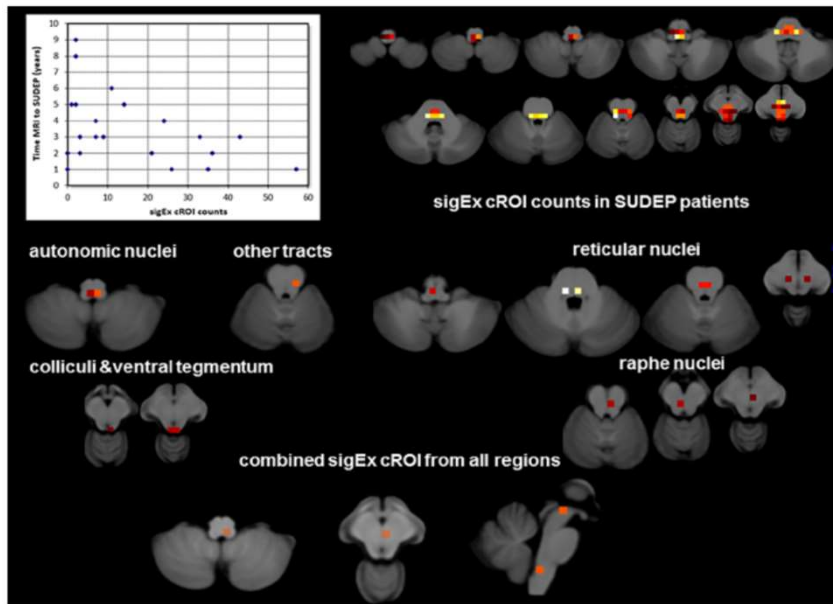
## Brainstem network disruption: A pathway to sudden unexplained death in epilepsy?

Susanne G. Mueller<sup>1</sup> | Maromi Nei<sup>2</sup> | Lisa M. Bateman<sup>3</sup> | Robert Knowlton<sup>4</sup>  
Kenneth D. Laxer<sup>5</sup> | Daniel Friedman<sup>6</sup> | Orrin Devinsky<sup>6</sup> | Alica M. Goldman<sup>7</sup>



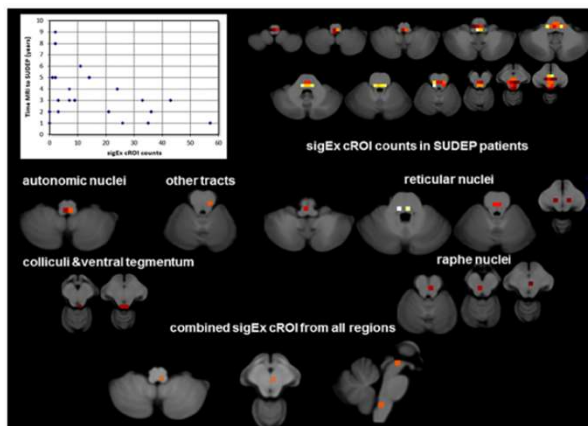
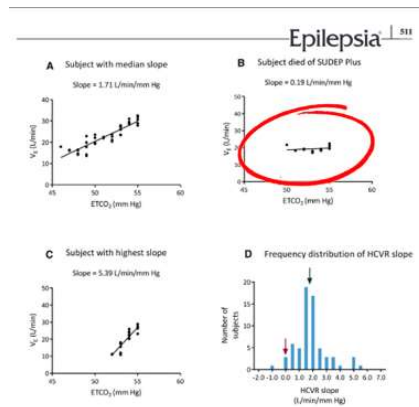
## The ventrolateral medulla and medullary raphe in sudden unexpected death in epilepsy

Smriti Patodia,<sup>1,2</sup> Alyma Somani,<sup>1,2</sup> Megan O'Hare,<sup>2,\*</sup> Ranjana Venkateswaran,<sup>1,2,\*</sup>  
Joan Liu,<sup>1,2,3</sup> Zuzanna Michalak,<sup>1,2</sup> Matthew Ellis,<sup>1</sup> Ingrid E. Scheffer,<sup>4</sup> Beate Diehl,<sup>2</sup>  
Sanjay M. Sisodiya<sup>2</sup> and Maria Thom<sup>1,2</sup>

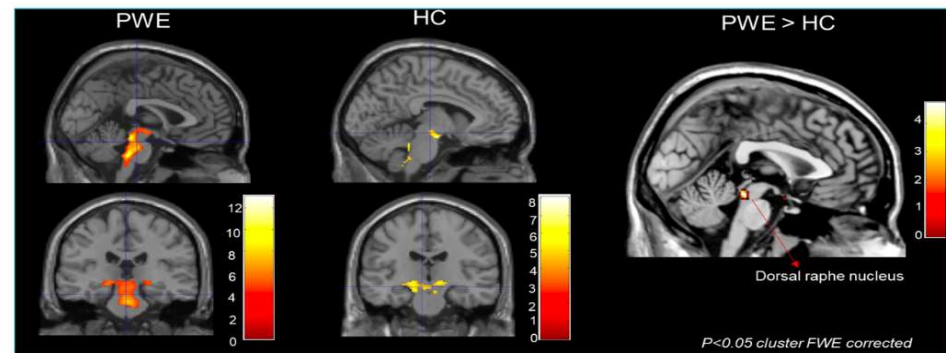


# Peri-ictal cardio-respiratory dysfunction

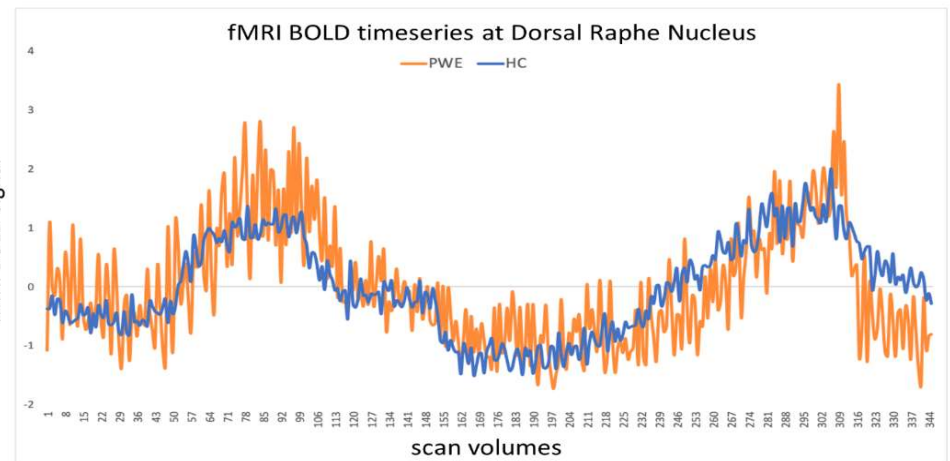
## e) Premortem identification of brainstem dysfunction



**B.**



**C.**





# Other types of cardio-respiratory dysfunction



Nellcor Oximax N-600x  
Covidien



Thoracic and abdominal belts  
Ambu Sleepmate RIPmate®



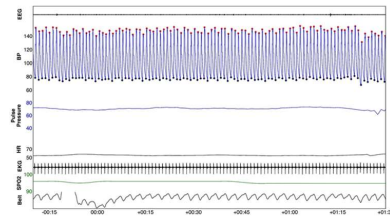
Thermocouple Airflow Sensor  
Pro-Tech



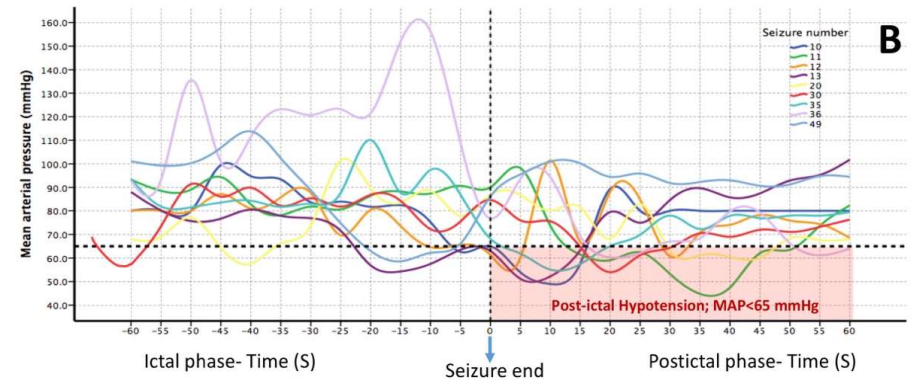
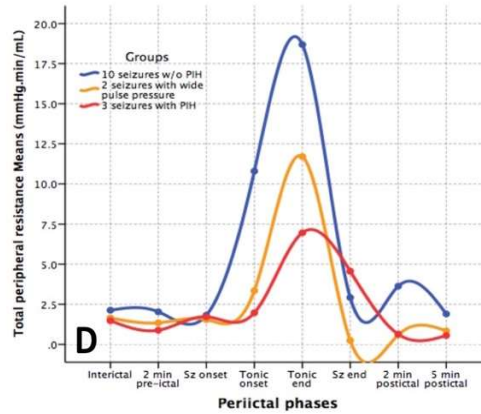
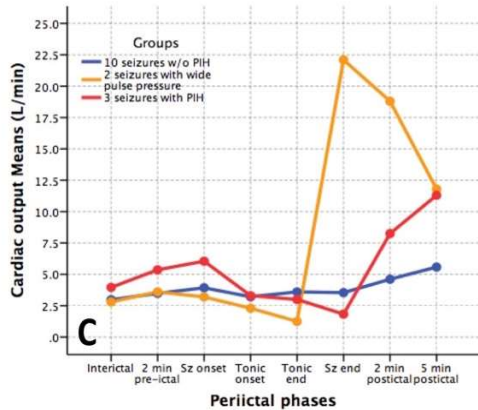
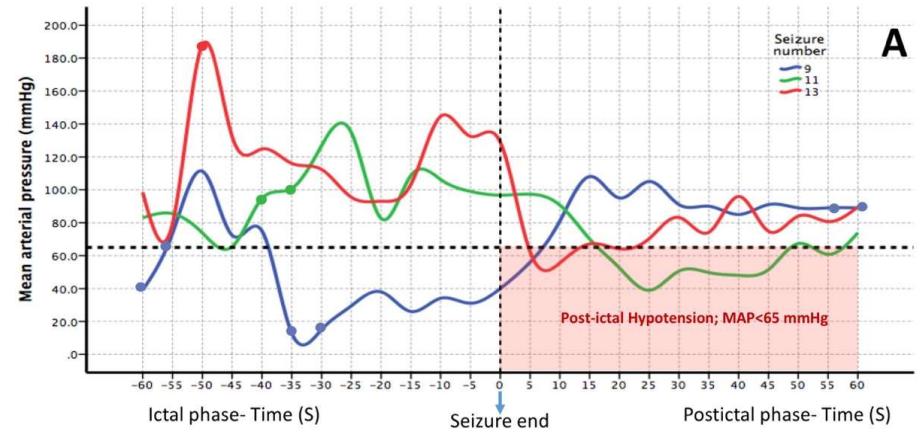
CNAP® Monitor 500  
CNSystems Medizintechnik AG



Capnograph Model 7900  
Philips



Digital tc-pCO<sub>2</sub> Sensor  
SenTec V-Sign™



# Cardio-respiratory Control and Modulation sites

## a) Location

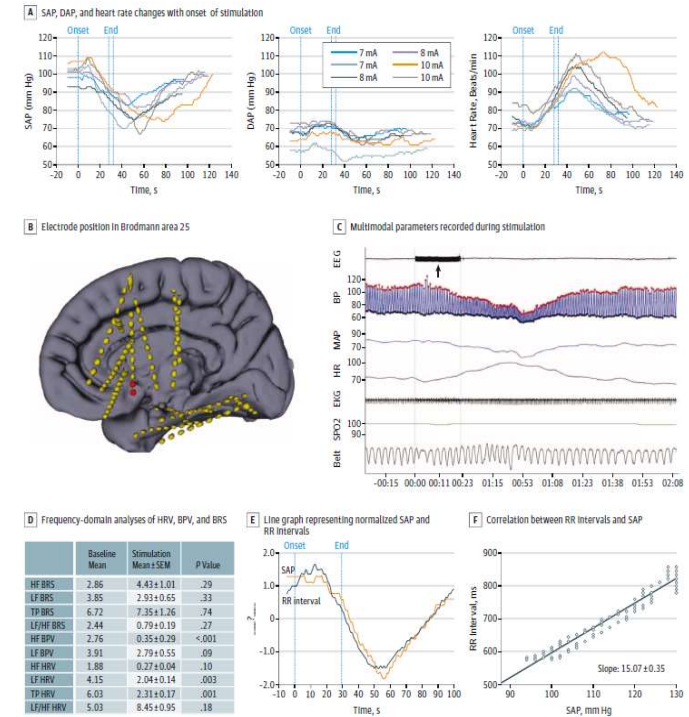
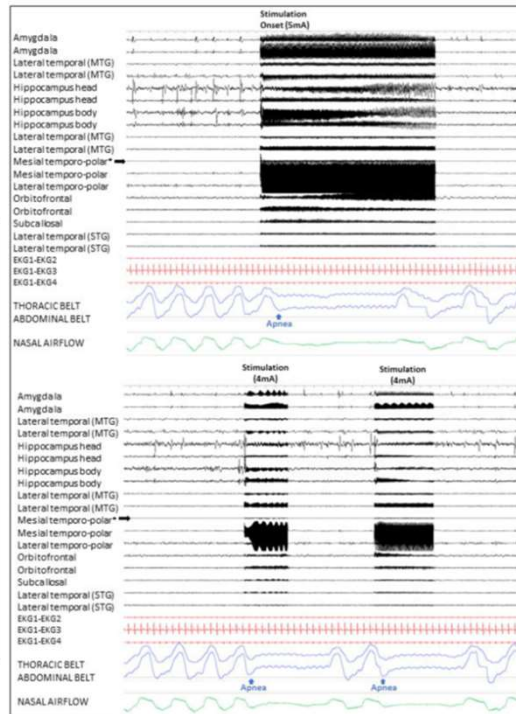
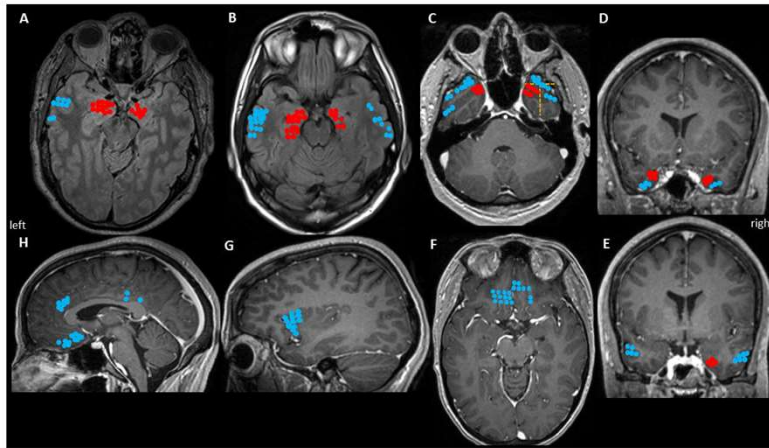
ARTICLE

### Limbic and paralimbic structures driving ictal central apnea

Nuria Lacuey, MD, Johnson P. Hampson, MSBME, Ronald M. Harper, PhD, Jonathan P. Miller, MD, and Samden Lhatoo, MD

Neurology® 2019;92:e655-e669. doi:10.1212/WNL.0000000000006920

**Correspondence**  
Dr. Lacuey  
nuria.lacuey@  
uhhospitals.org

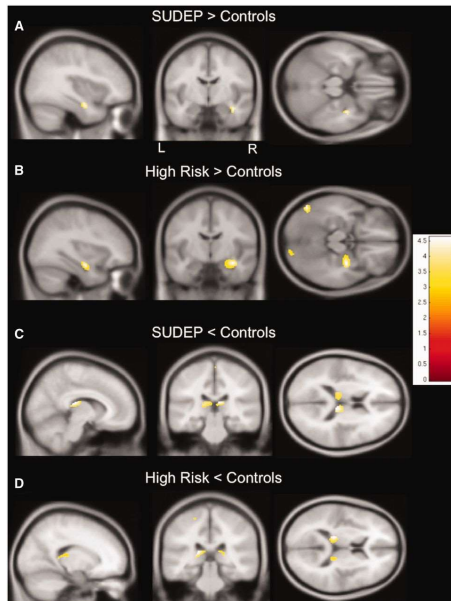


# Cardio-respiratory Control and Modulation sites

## b) Damage

### Structural imaging biomarkers of sudden unexpected death in epilepsy

Britta Wandschneider,<sup>1,2</sup> Matthias Koepp,<sup>1,2</sup> Catherine Scott,<sup>1,2</sup> Caroline Micallef,<sup>1,2</sup> Simona Balestrini,<sup>1,2,3</sup> Sanjay M. Sisodiya,<sup>1,2,4</sup> Maria Thom,<sup>1,2,4</sup> Ronald M. Harper,<sup>4,5</sup> Josemir W. Sander,<sup>1,2,4,6</sup> Sjoerd B. Vos,<sup>1,2,7</sup> John S. Duncan,<sup>1,2</sup> Samden Lhatoo<sup>4,8</sup> and Beate Diehl<sup>1,2,4</sup>



### Neuroimaging of Sudden Unexpected Death in Epilepsy (SUDEP): Insights From Structural and Resting-State Functional MRI Studies

Luke A. Allen<sup>1,2,7</sup>, Ronald M. Harper<sup>3,4,5</sup>, Samden Lhatoo<sup>3,6</sup>, Louis Lemieux<sup>1,2</sup> and Beate Diehl<sup>1,2,3</sup>

<sup>1</sup>Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, United Kingdom

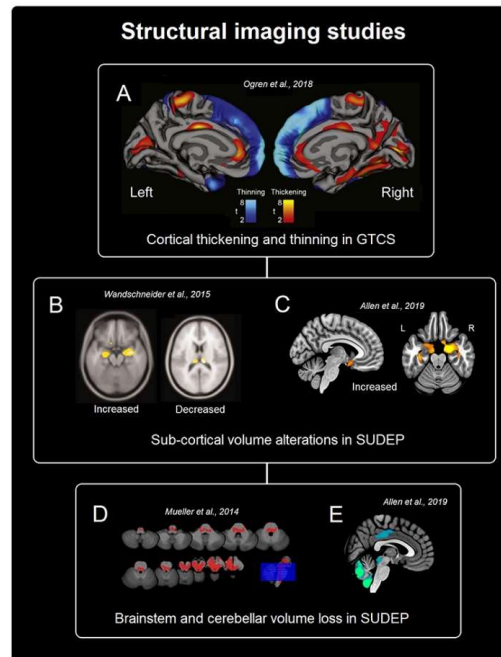
<sup>2</sup>Epilepsy Society MRI Unit, Chalfont St Peter, London, United Kingdom

<sup>3</sup>The Center for SUDEP Research, National Institute of Neurological Disorders and Stroke, Bethesda, MD, United States

<sup>4</sup>Department of Neurobiology, David Geffen School of Medicine at UCLA, University of California, Los Angeles, Los Angeles, CA, United States

<sup>5</sup>Brain Research Institute, University of California, Los Angeles, Los Angeles, CA, United States

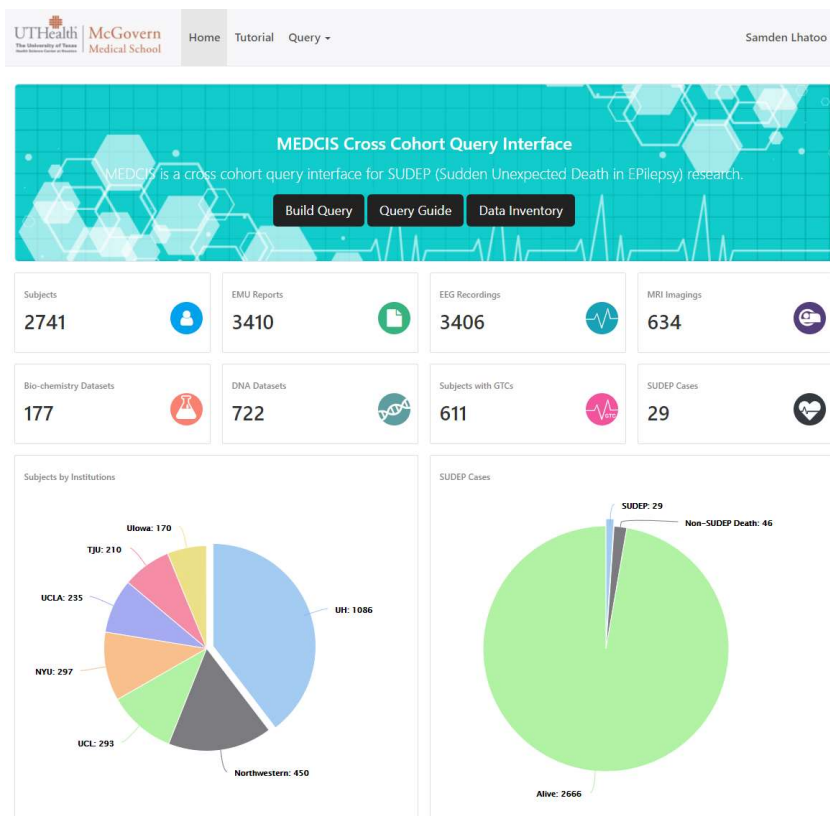
<sup>6</sup>Department of Neurology, University of Texas Health Sciences Center at Houston, Houston, TX, United States



## Key Findings

- Premortem risk may be indicated by prolonged ictal central apnea, post-convulsive central apnea  $\pm$  bradycardia, abnormal HCVR, (PGES)
- Abnormal peri-ictal cardiorespiratory responses indicate brainstem dysfunction
- There are both structural (MRI and neuropathology) and functional (fMRI/HCVR) indicators of brainstem damage in persons with epilepsy
- There is temporal accrual of risk - more damage/dysfunction is seen with long duration of epilepsy, and/or proximity to death
- Identification of cardio-respiratory modulation sites in the human brain; some of these sites suggest potential for neuromodulation, breathing rescue and targeted SUDEP prevention
- Strong evidence of brainstem contributions to SUDEP
- Case control prospective study .....

# The CSR Informatics and Data Analytics Core



**UTHealth McGovern Medical School** Home Tutorial Query - Samden Lhatoo -

## MEDCIS Cross Cohort Query Interface

MEDCIS is a cross cohort query interface for SUDEP (Sudden Unexpected Death in Epilepsy) research.

[Build Query](#) [Query Guide](#) [Data Inventory](#)

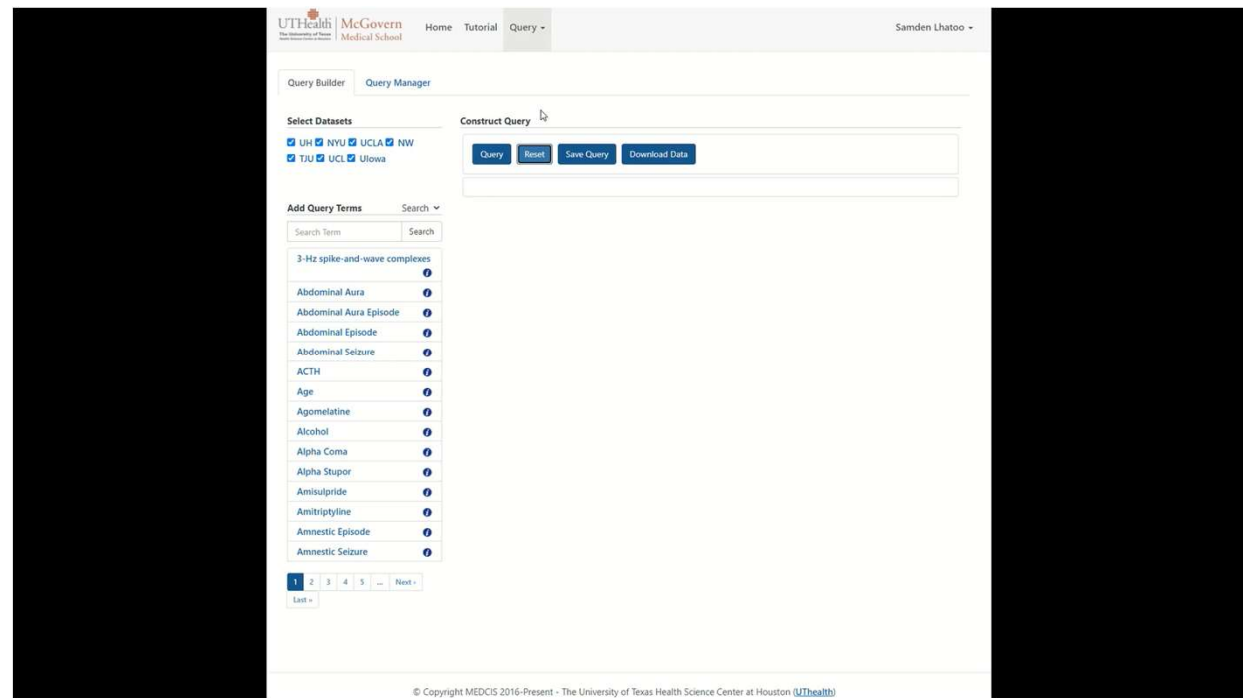
Subjects 2741	EMU Reports 3410	EEG Recordings 3406	MRI Imagings 634
Bio-chemistry Datasets 177	DNA Datasets 722	Subjects with GTCs 611	SUDEP Cases 29

**Subjects by Institutions**

Institution	Count
UW: 1086	1086
Northwestern: 450	450
UCL: 293	293
NYU: 297	297
UCLA: 235	235
TJU: 210	210
Ulowa: 170	170

**SUDEP Cases**

Status	Count
Alive	2666
SUDEP	29
Non-SUDEP Death	46



**UTHealth McGovern Medical School** Home Tutorial Query - Samden Lhatoo -

Query Builder Query Manager

**Select Datasets**

UH  NYU  UCLA  NW  
 TJU  UCL  Ulowa

**Construct Query**

[Query](#) [Reset](#) [Save Query](#) [Download Data](#)

**Add Query Terms** Search

Search Term Search

- 3-Hz spike-and-wave complexes
- Abdominal Aura
- Abdominal Aura Episode
- Abdominal Episode
- Abdominal Seizure
- ACTH
- Age
- Agomelatine
- Alcohol
- Alpha Coma
- Alpha Stupor
- Amisulpride
- Amisulpride
- Amisulpride
- Amisulpride
- Amisulpride
- Amisulpride
- Amisulpride

1 2 3 4 5 ... Next

1 2 3 4 5 ... Next

© Copyright MEDCIS 2016-Present - The University of Texas Health Science Center at Houston (UTHealth)

# Current CSR Database-related Projects



**David Auerbach PhD**  
Prevalence and  
triggers for ECG  
abnormalities and  
arrhythmias in  
patients with epilepsy  
CURE 2021



**Nuria Lacuey MD PhD**  
Defining Breathing  
Network  
Neuromodulatory  
Approaches for  
Prevention of SUDEP  
CURE 2020



**Rup Sainju MD**  
CO2 Responses in  
SUDEP  
CURE 2016



**Licong Cui PhD**  
An informatics  
framework for SUDEP  
Risk Marker  
Identification and Risk  
Assessment  
NINDS 5R01NS116287



Baylor College of  
Medicine



Case Western Reserve  
University



Ann & Robert H. Lurie  
Children's Hospital of  
Chicago



Columbia University



Harvard University



New York University



Northwestern University



Texas Children's  
Hospital



Thomas Jefferson  
University



University of California  
Los Angeles



University of California  
San Francisco



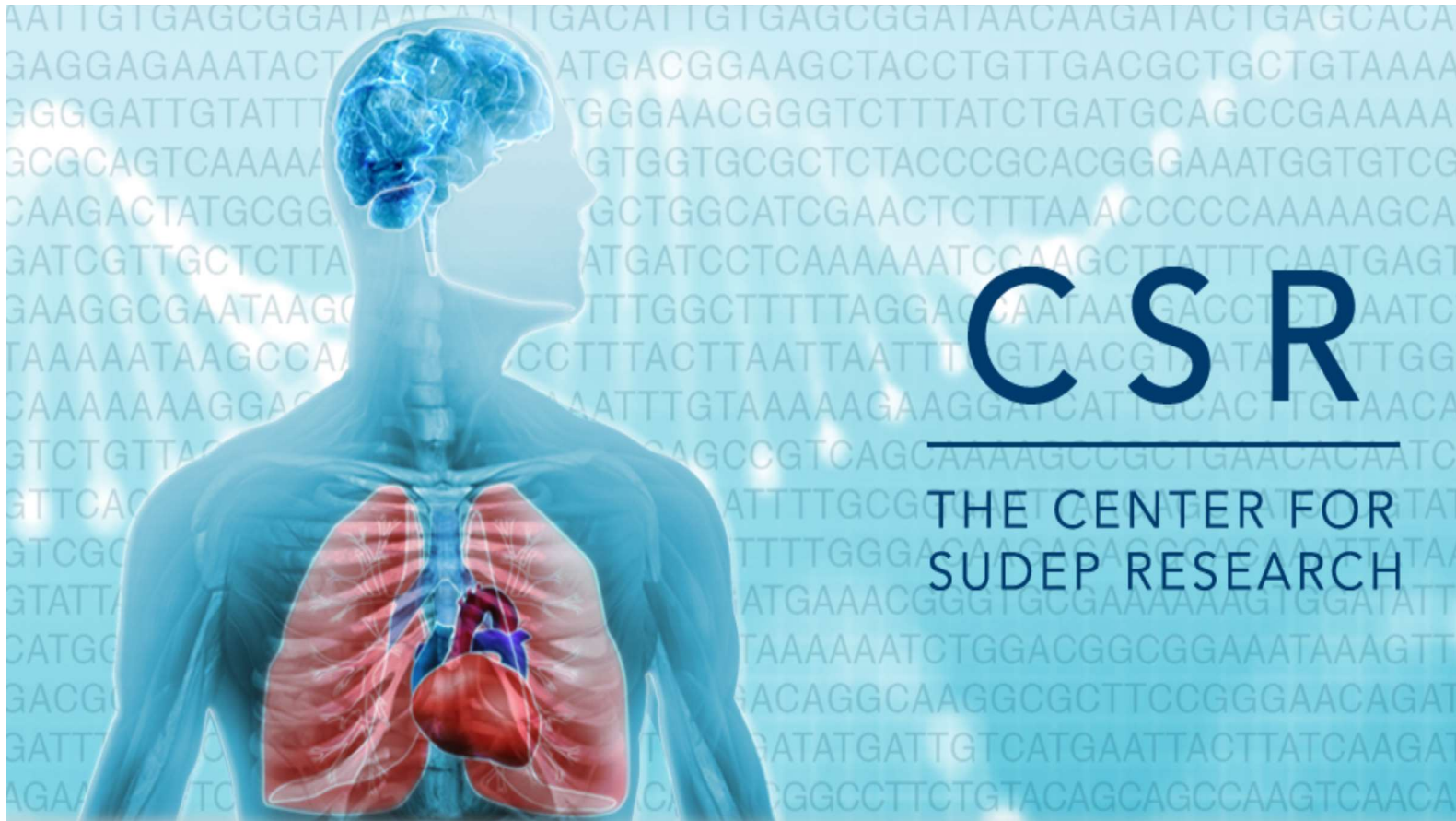
University College  
London



University of Iowa



University of Michigan



**CSR  
Clinical  
Projects  
and  
Cores**

**Sam Lhatoo  
MD FRCP**