SUDEP Research Update

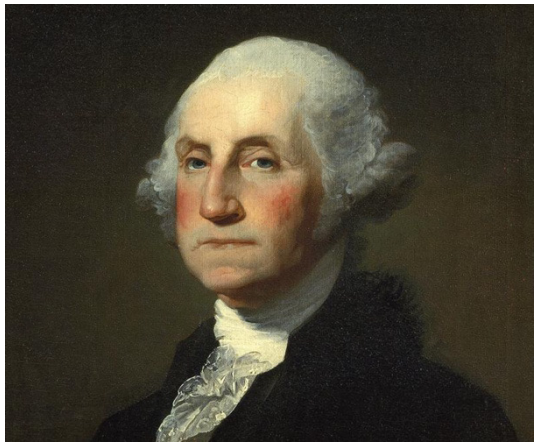
Sam Lhatoo MD FRCP(Lon)

DEE-P CONNECTIONS

NIH National Institute of Neurological Disorders and Stroke

CSR THE CENTER FOR SUDEP RESEARCH

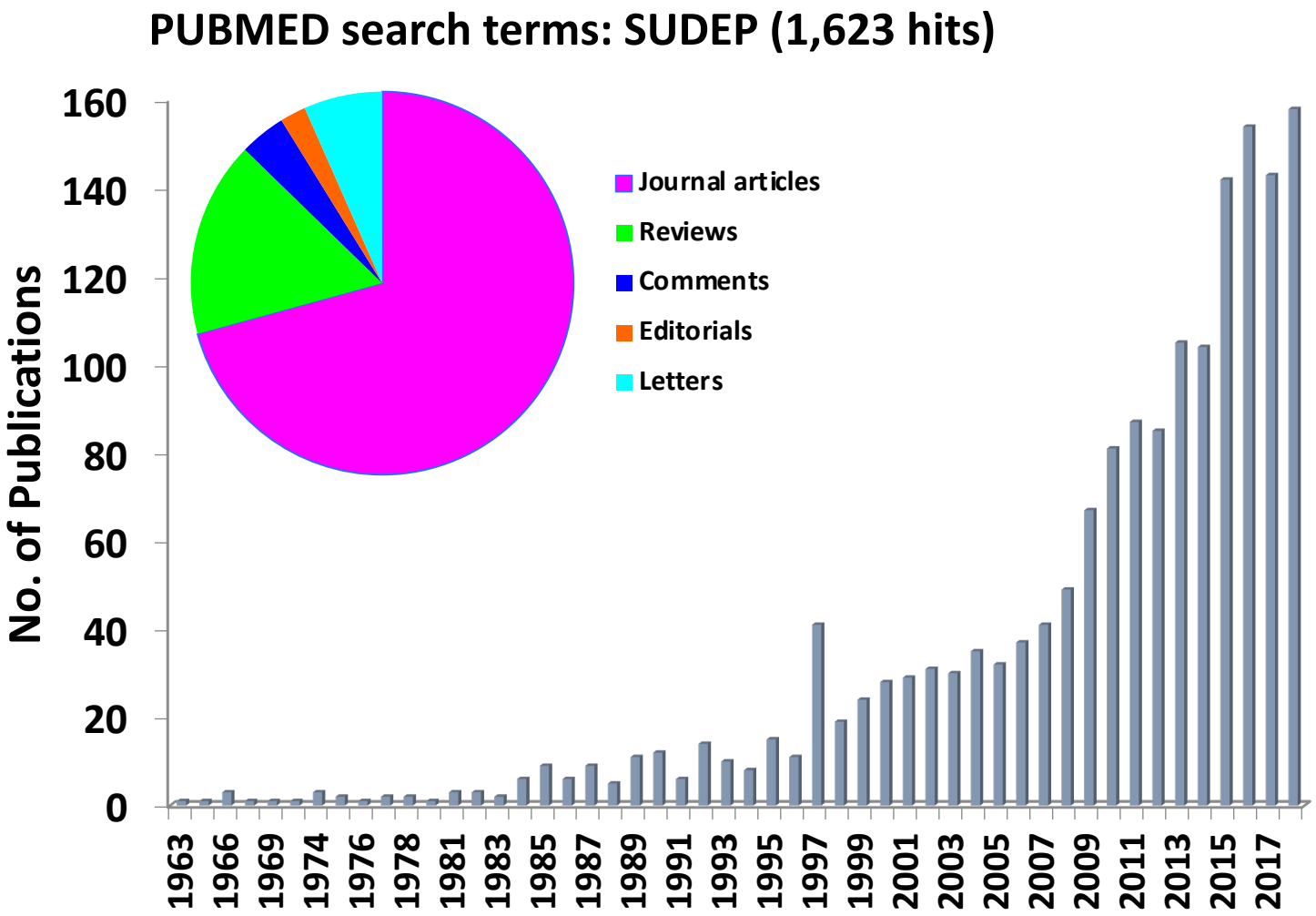
timeline



"She rose from dinner about four o'clock in better health and spirits than she appeared to have been in for some time; soon after which she was seized with one of her usual fits, and expired in it, in less than two minutes without uttering a word, a groan, or scarce a sigh."
….1773 AD

- 1773: George Washington's account
- 1975: First large SUDEP report (37 cases)
- 1997: Definitions agreed
- 2013: MORTEMUS report
- 2015: SUDEP Center Without Walls

Researching the Problem

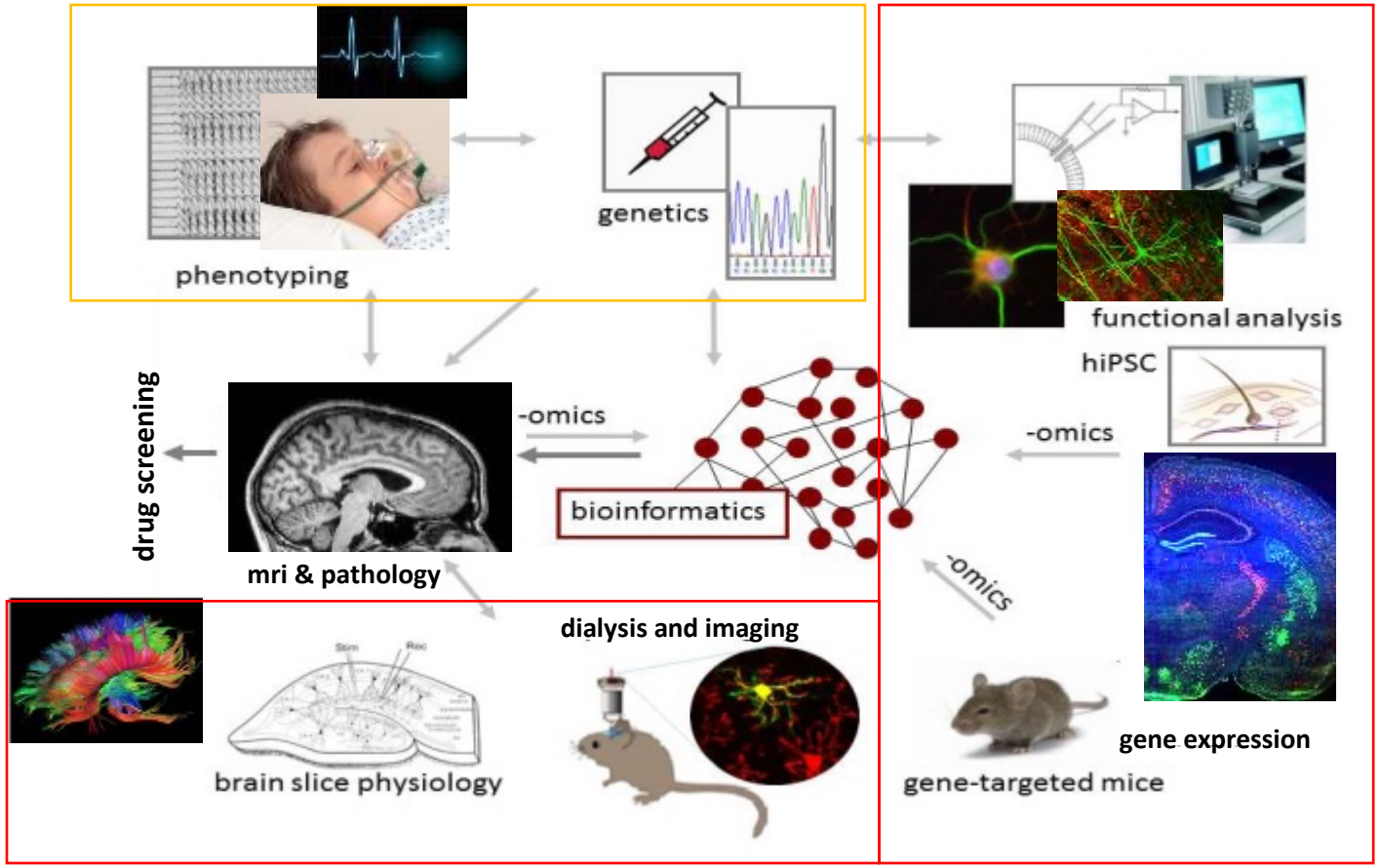


NINDS Center for SUDEP Research (CSR)

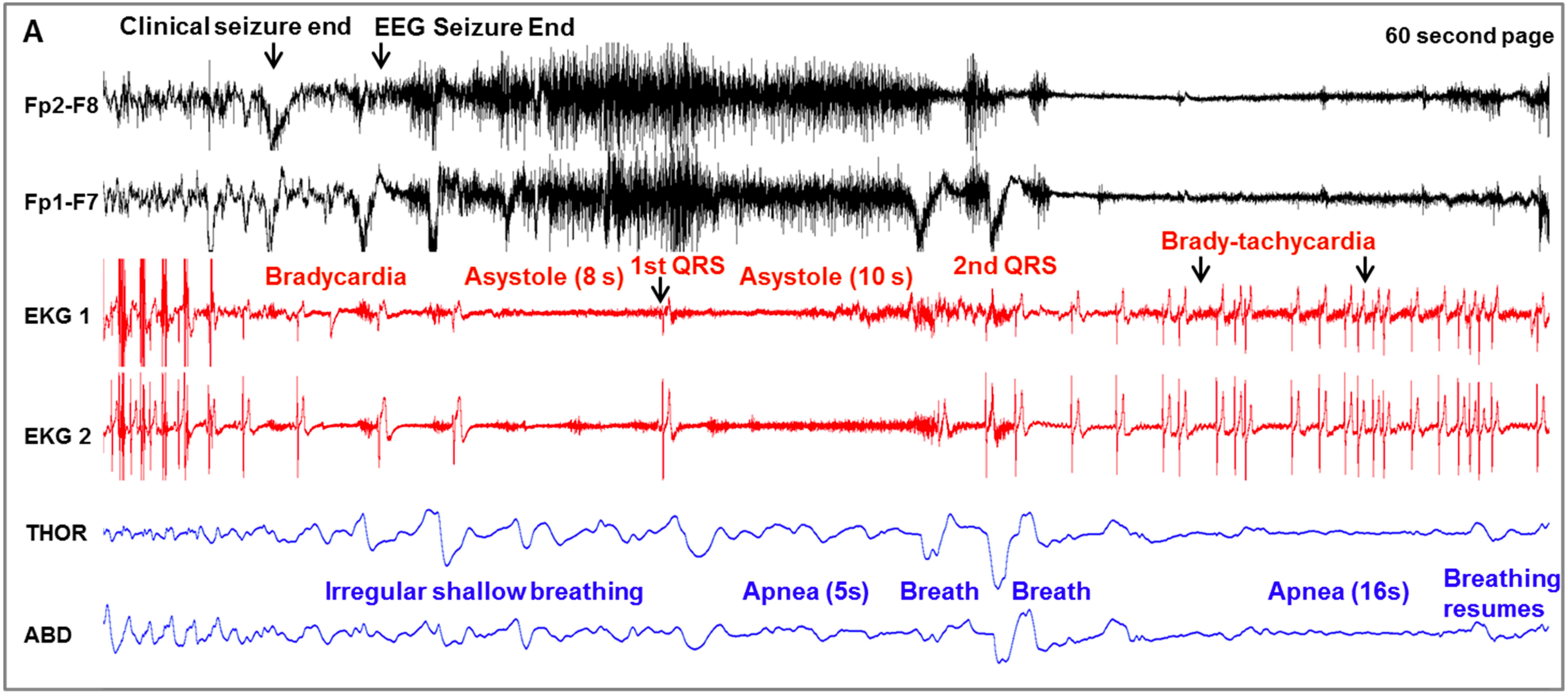
Predictive genes, clinical biomarkers and basic mechanisms of SUDEP

Baylor College of Medicine
Case
Columbia
Harvard
Jefferson
MIT
NYU
UCSF
UCLA
UC London
U. Chicago Lurie
U. Michigan
U. Iowa

Over 85 investigators!



A Case of near-SUDEP

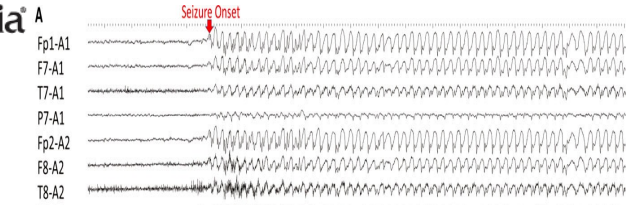


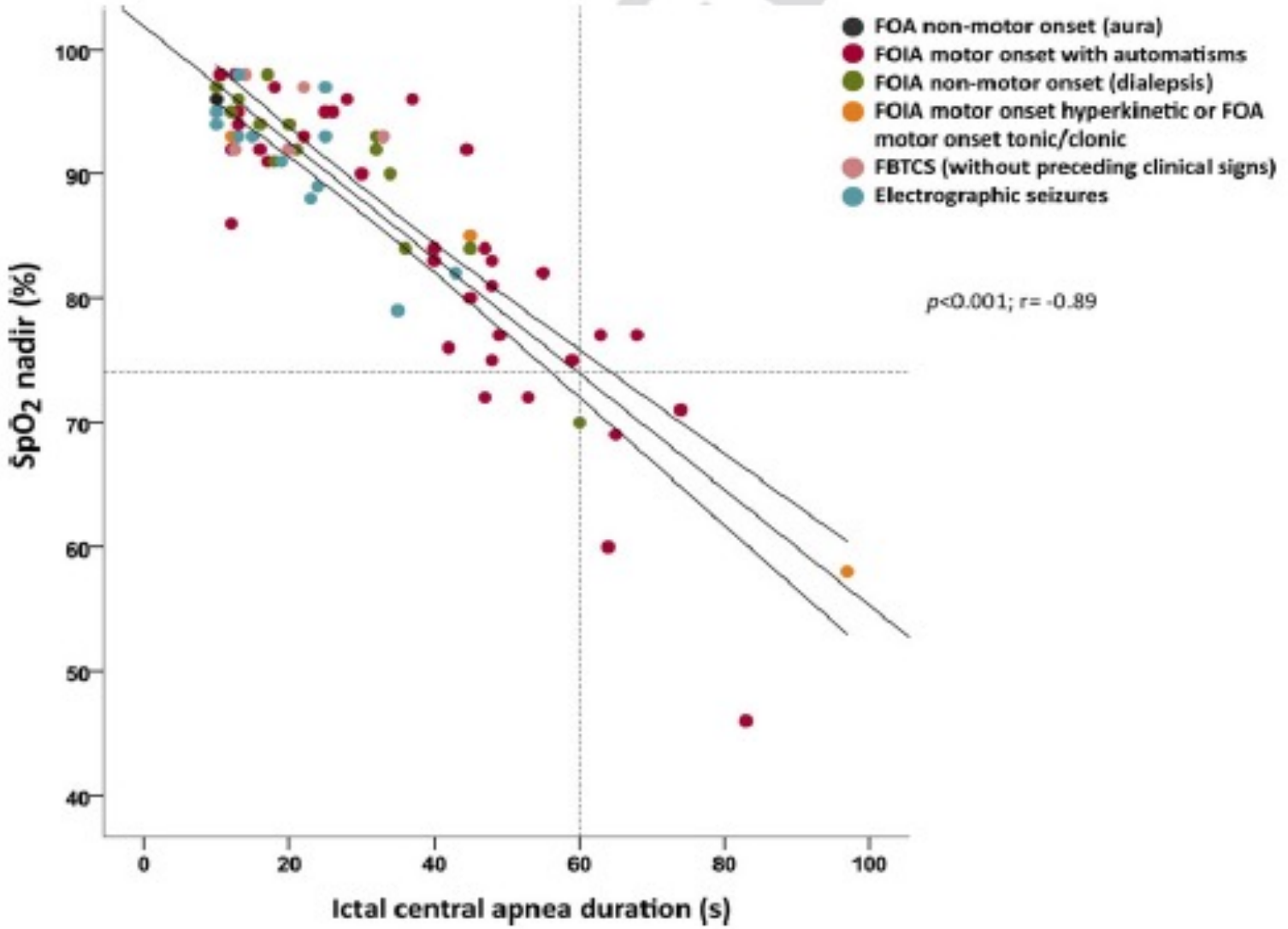
1. Ictal Central Apnea (stoppage of breathing during seizures)

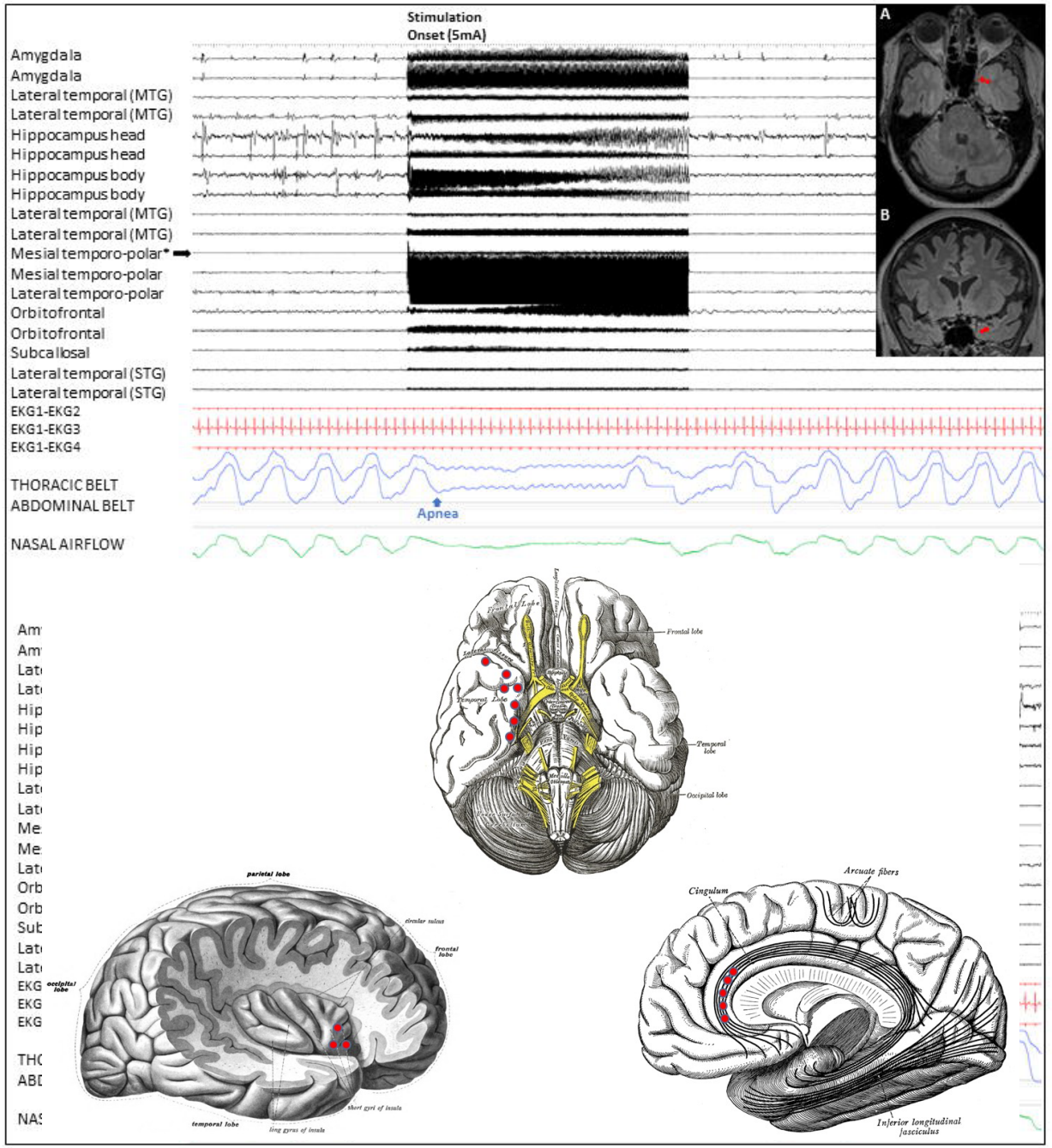
FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

The incidence and significance of periictal apnea in epileptic seizures







- Certain brain structures control breathing
- Seizures spreading to such structures paralyze function and prevent breathing
- Stimulating function may be a means to preventing death

2. Post-convulsive Central Apnea (cessation of breathing after a convulsion)

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 Nei, MD, Kingman Strohl, MD, Catherine Scott, MPHil, Brian K. Gehlbach, MD, Bilal Zonjy, MD, Norma J. Hupp, Anita Zaremba, BA, Nassim Shafiabadi, 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

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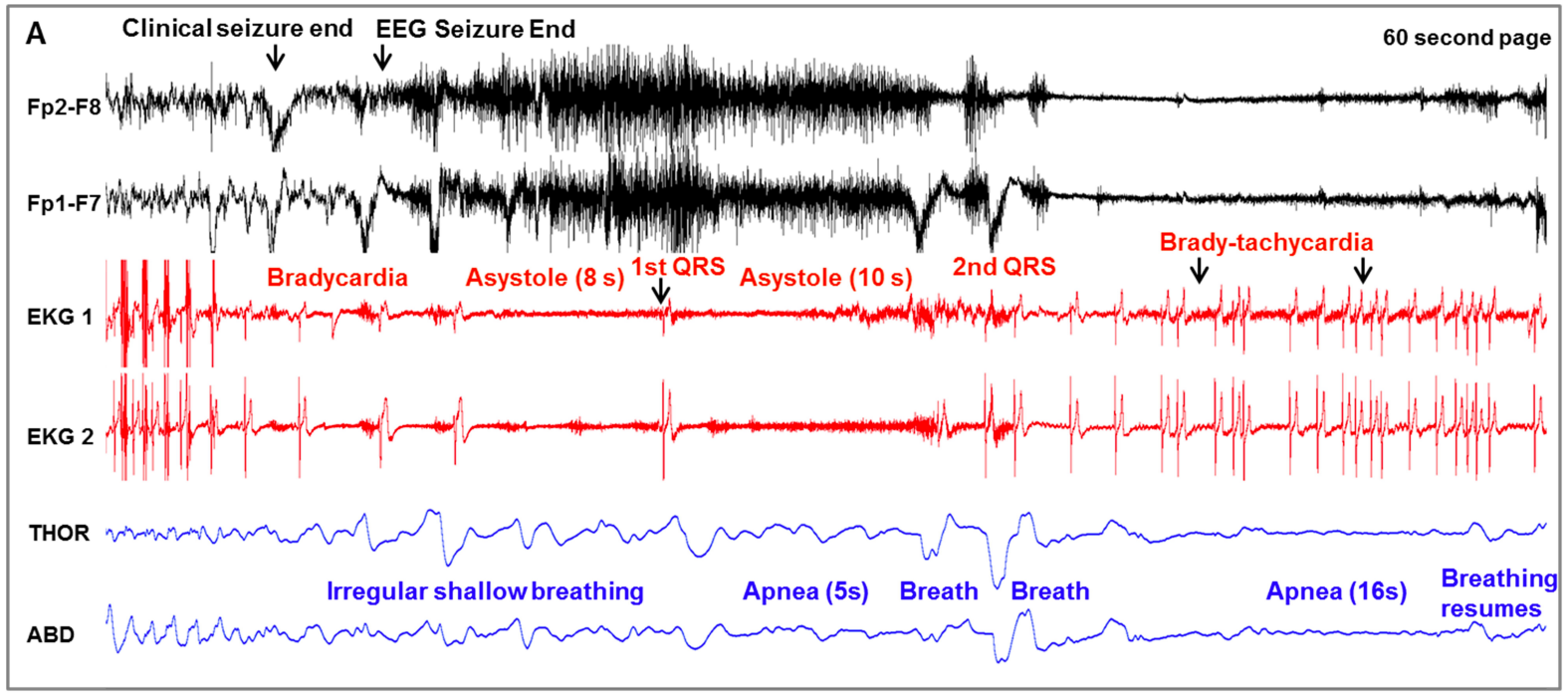
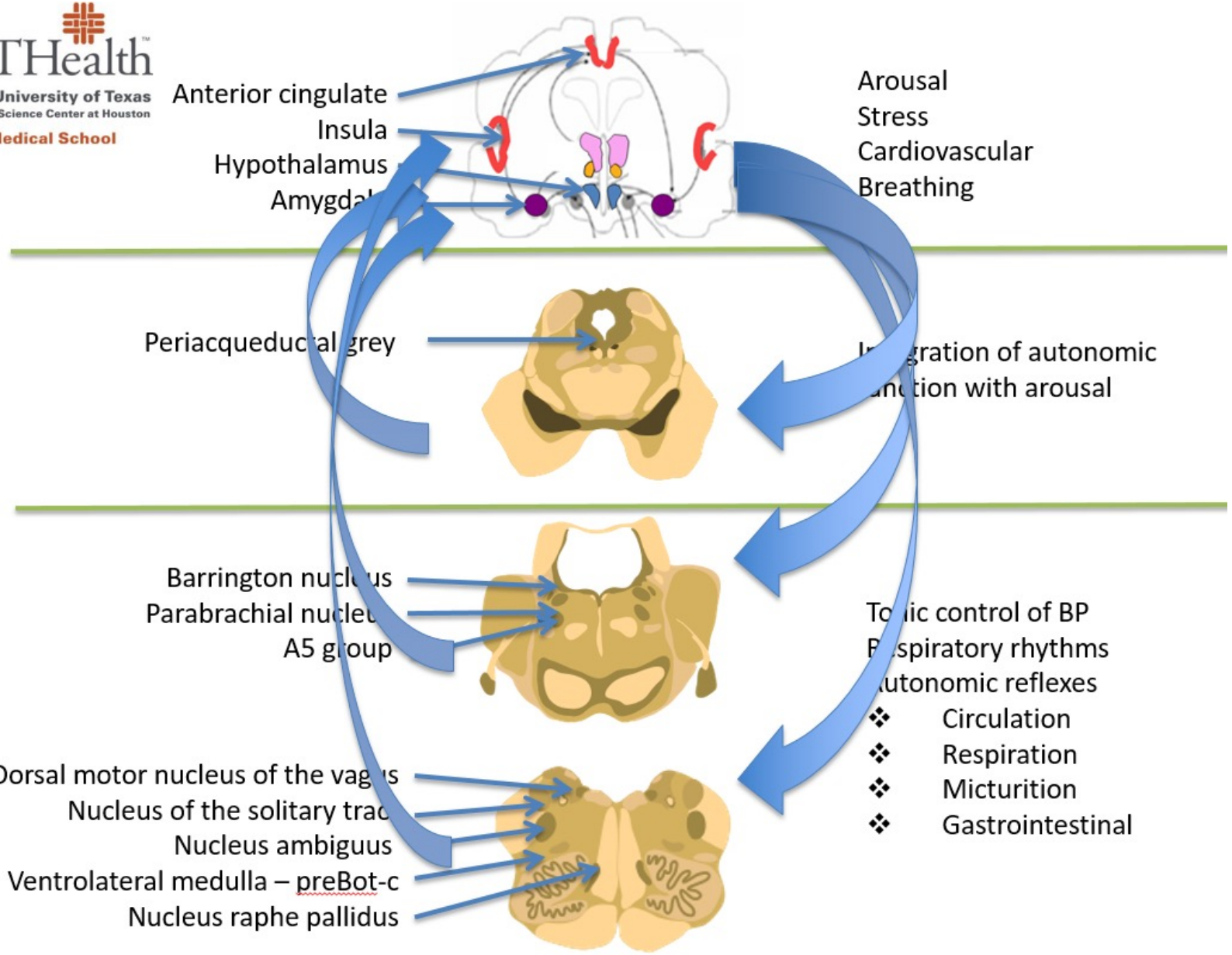


UTHealth
The University of Texas
Health Science Center at Houston
Medical School

3. Role of the Brainstem



3. Role of the Brainstem

FULL-LENGTH ORIGINAL RESEARCH

Ventilatory response to CO_2 in patients with epil

Rup K. Sainju[1] | Deidre N. Dragon[1] | Harold B. Winnike[2] | Marc
Mark A. Granner[1] | Brian K. Gehlbach[1,4] | George B. Richerson[1,5]

ARTICLE

Postictal serotonin levels are a ictal apnea

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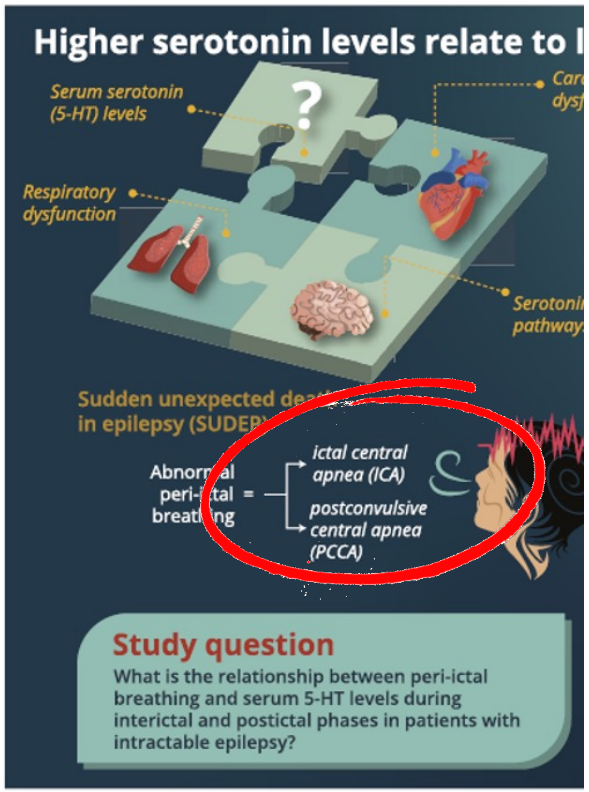
Johnson P. Hampson, MS, Carl L. Faingold, PhD, Daniel Friedman, MD, Orrin Devinsky,
Rup K. Sainju, MBBS, Stephan Schuele, MD, MPH, Beate Diehl, MD, PhD, FRCP, Maromi
Ronald M. Harper, PhD, Lisa M. Bateman, MD, George Richerson, MD, PhD, and Samder

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



doi:10.1093/brain/awy078 BRAIN 2018: 141; 1719–1733 | 1719
BRAIN
A JOURNAL OF NEUROLOGY

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

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

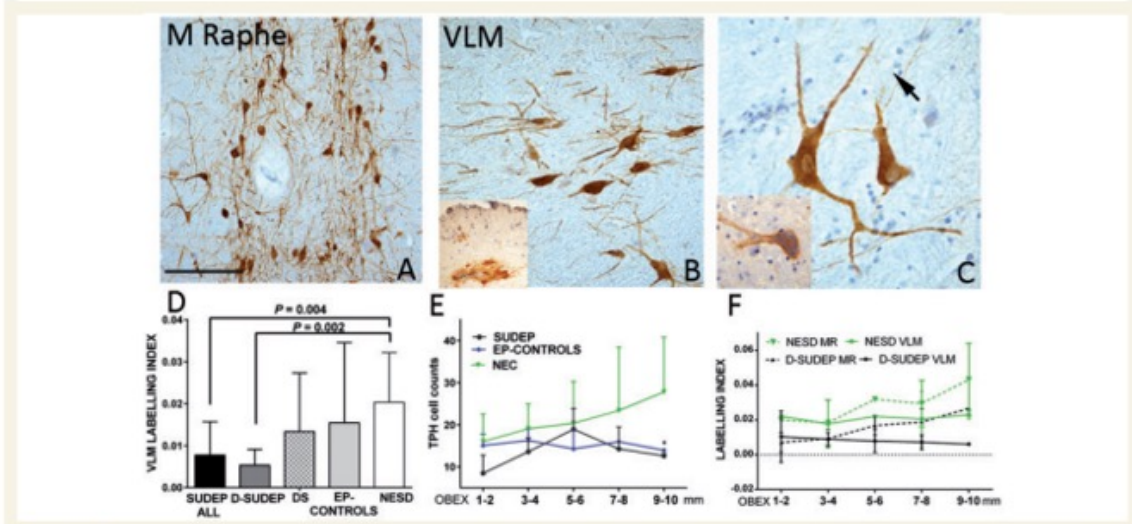
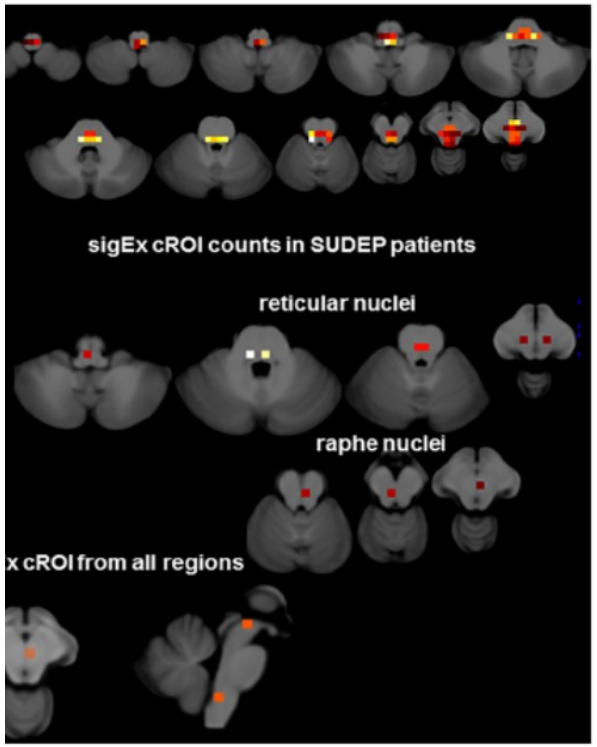


Figure 3 Serotonergic neurons. (**A**) Tryptophan hydroxylase (TPH2) labelling in the median raphe showing distinct neuronal labelling and processes. (**B**) In the VLM, reduced density of neurons were noted (inset cluster of neurons in the floor of the fourth ventricle were occasionally also noted). (**C**) TPH2-positive neurons and coarse dendrites in VLM with occasional fine axon crossing in the background (arrow). Inset: TPH2 positive neurons in VLM with more peripheral labelling pattern was occasionally noted. (**D**) Bar chart showing the differences in labelling index between the groups in the VLM, which was significantly lower in SUDEP groups than non-epilepsy controls. (**E**) Line graph of mean TPH2 cell counts between groups (mean values and standard deviation show as error bars) in the VLM with obex intervals were lower for the SUDEP and epilepsy controls than non-epilepsy controls (NEC) at all levels, with the greatest statistical difference noted between all epilepsy cases and controls at obex 9–10 mm ($P = 0.034$). (**F**) Line graph of TPH2 labelling in medullary raphe and VLM (shown as dashed lines and single lines, respectively) of mean values (and error bars representing standard deviations) with respect to obex levels for definite SUDEP and non-epilepsy sudden death controls (NESD). A positive correlation of medullary raphe labelling index with more rostral obex levels ($P = 0.01$) was noted and lower labelling index in SUDEP than NESD. Magnifications: photomicrographs with ×10 (**A**), ×20 (**B**) and ×40 objective lenses. Scale bar in **A** = 300 μm in **A**, 200 μm in **B**, and 90 μm in **C**.

uption: A pathway to sudden ilepsy?

ei[2] | Lisa M. Bateman[3] | Robert Knowlton[4] |
an[6] | Orrin Devinsky[6] | Alica M. Goldman[7]



4. Spreading depression

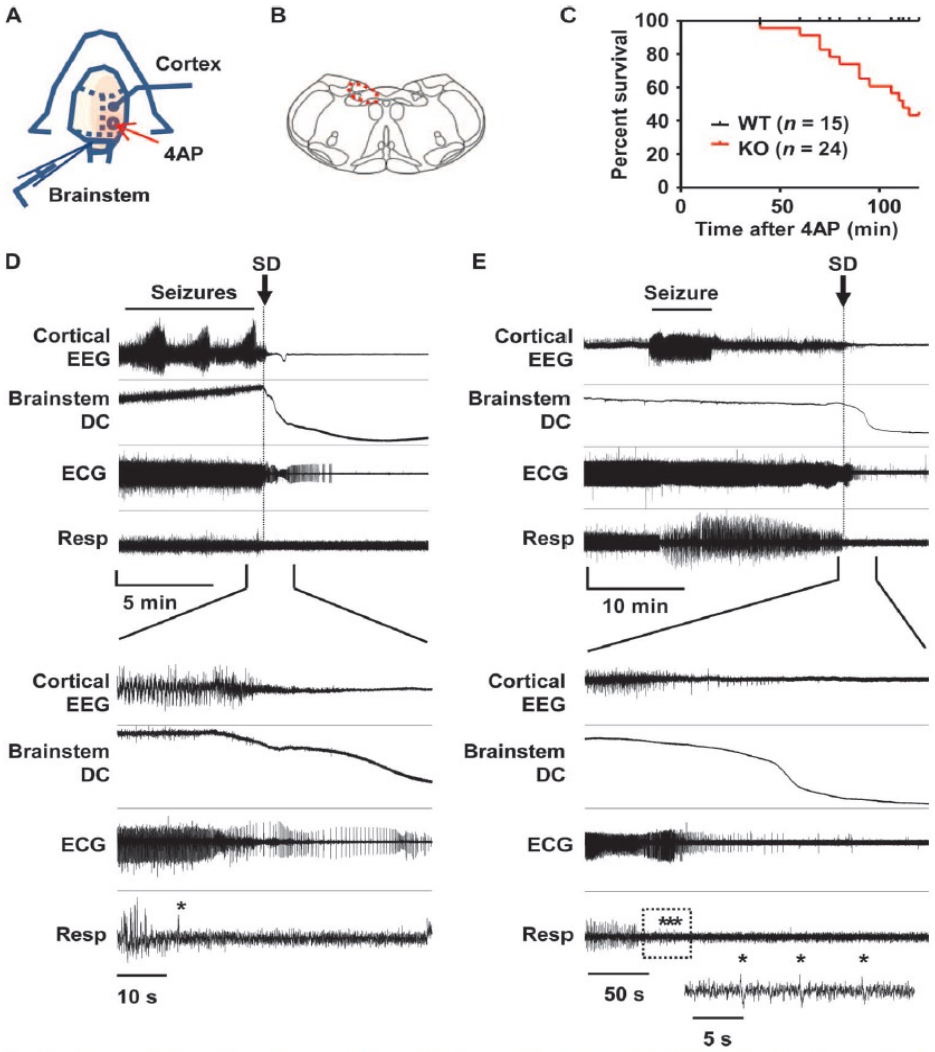


Fig. 1. Premorbid cardiorespiratory dysregulation and brainstem SD in Kv1.1 mutant associated with cortical seizures in vivo. (**A**) Diagram of experimental setup for application of 4AP and recording of EEG and brainstem DC potentials in spontaneously breathing urethane-anesthetized juvenile mice (P18 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 premorbid 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.

Spreading depolarization in the brainstem mediates sudden cardiorespiratory arrest in mouse SUDEP models

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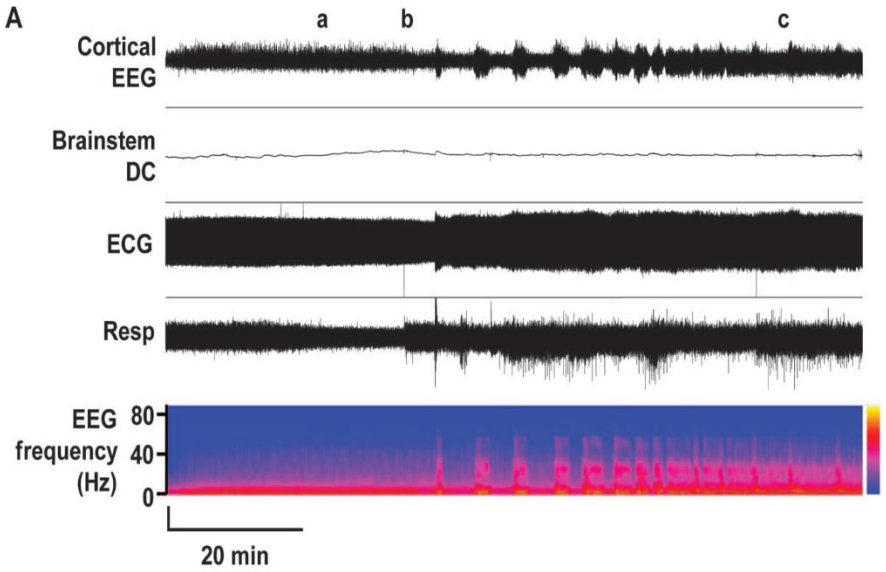

5. Genetic Risk?

Kcnq1
Kcna1
Scn1a
Scn1b
Scn8a
Cacna1a
a2Na-K-ATPase
Senp2
5HT2cR
Ryr2
Ank3
A2 spectrin
ßIV spectrin

- No evidence that SUDEP is familial
- There may/may not be a genetic predisposition
- Certain gene disorders carry higher risk
  - e.g. Dravet's Syndrome
- Some genetic disorders that cause sudden death co-exist with epilepsy
  - e.g. Long-QT Syndrome

6. Intervention – where are we?

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 Nei, Ronald M. Harper, PhD, Lisa M. Bateman, MD, George Richerson, MD, PhD, and Samden D. Lhatoo, MD, FRCP

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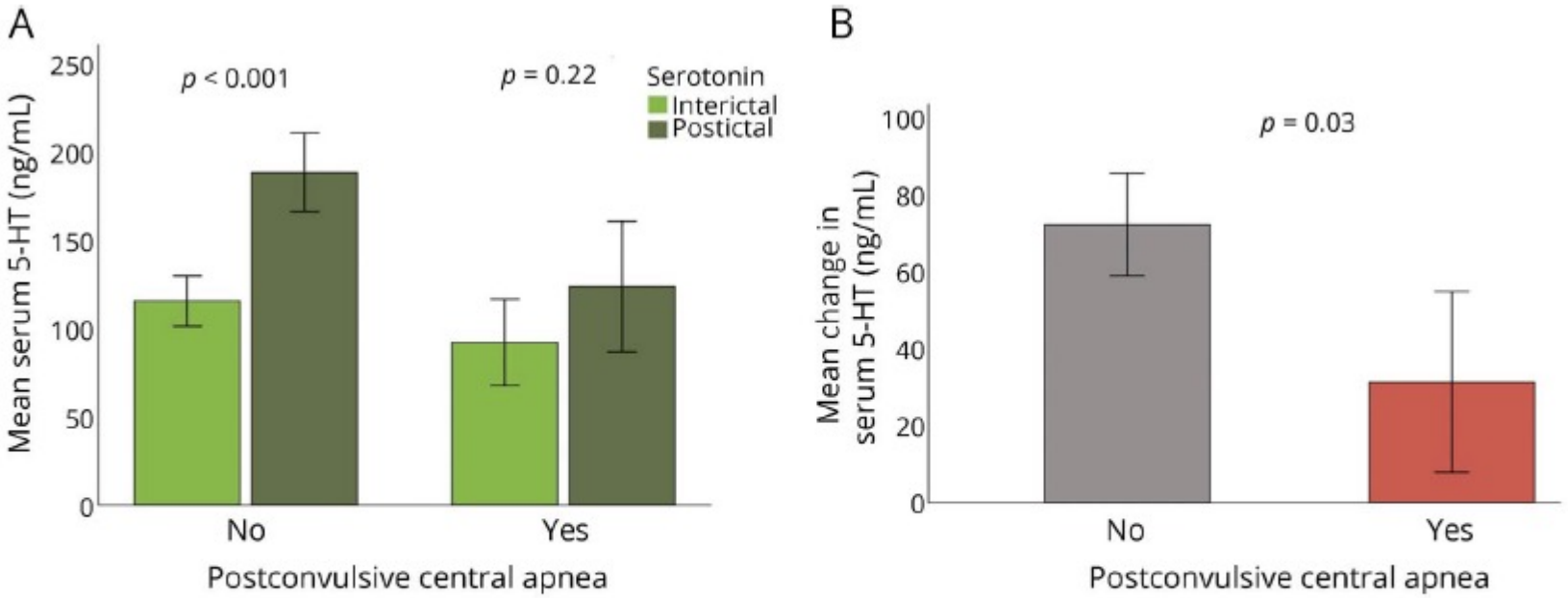

(A) Elevated levels of postictal 5-HT in generalized convulsive seizures (GCS). The mean serum interictal 5-HT levels are shown in light green bars and postictal 5-HT levels (ng/mL) are shown in dark green bars for the 2 seizure groups: PCCA (n = 8) and non-PCCA (n = 19). The levels of postictal serum 5-HT in the absence of PCCA were higher when compared to interictal levels ($p < 0.001$), but not when PCCA occurred ($p = 0.22$). (B) Elevated serum 5-HT levels in the absence of PCCA. The change in 5-HT (postictal minus interictal) was plotted for seizures without PCCA (in gray) and with PCCA (in red). The change in serum 5-HT (postictal minus interictal levels) was moderate when the 2 groups were compared ($p = 0.03$).

ARTICLE

Temporal trends and autopsy findings of SUDEP based on medico-legal investigations in the United States

Esma Cihan, MD, Orrin Devinsky, MD, Dale C. Hesdorffer, PhD, Michael Brandsoy, Ling Li, MD, David R. Fowler, MB ChB, Jason K. Graham, MD, Michael W. Karlovich, Jaclyn E. Yang, Anne E. Keller, MPH, Elizabeth J. Donner, MD, and Daniel Friedman, MD, MSc

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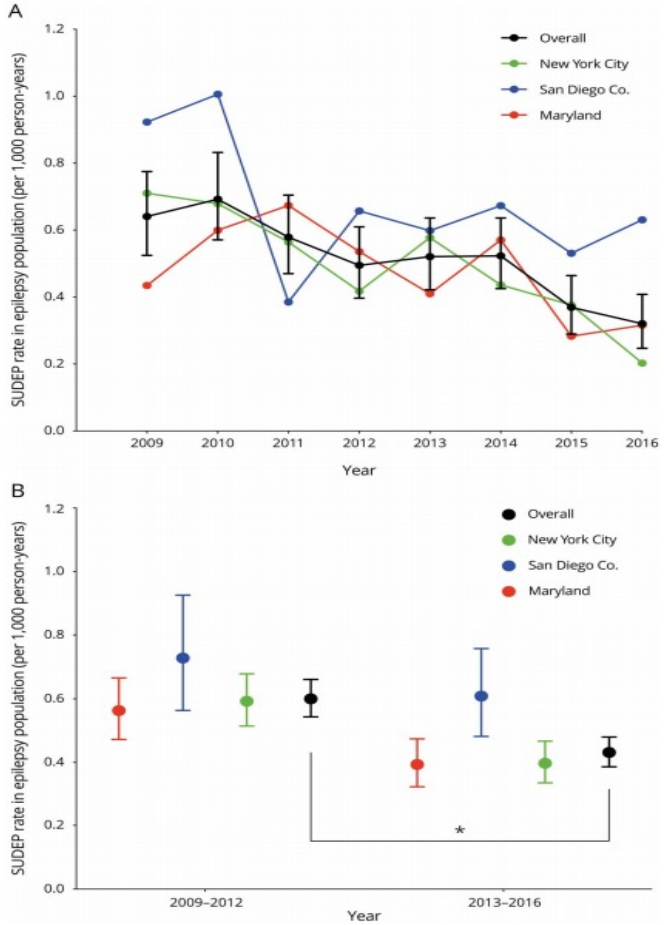

(A) There was a decreasing monotonic trend in ME-investigated SUDEP incidence ($z = -2.2$, $S = -42$, $p = 0.028$) in 3 regions in 2009–2016. (B) There was a 28% reduction in ME-investigated SUDEP incidence in 3 regions in 2013–2016 compared to 2009–2012 (confidence interval, 17%–38%; $p < 0.0001$).

7. Some things may be working

- There was a 28% reduction in medical examiner reported SUDEP in 3 regions (NYC, San Diego County, Maryland) comparing 2009-2012, and 2013-2016
- Population level effects – awareness Education, urgency of treatment

Conclusions

- SUDEP research is thriving
- We understand seizure related breathing and cardiac dysfunction better than ever before
- We are able to fine tune risk better than before
- We are close to a SUDEP risk-index for individualizing susceptibility
- Understanding processes is opening up the way for targeted intervention
- Awareness of SUDEP and prioritizing/striving for seizure freedom may be reducing incidence
- Stopping seizures is still the best way to reduce risk