Focal Cooling for the Prevention and Treatment of Epilepsy:
From Patients to Models (and back again)

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Patents:
Learning Objectives

• Efficacy of cooling on seizures in humans and models
• Efficacy of cooling as an anti-epileptogenic agent
• Explore necessary ΔT
• Introduce potential implanted cooling devices
Outline

• Clinical observations supporting the pursuit of cooling-based therapies for epilepsy
• Implementation: problems and solutions
• Focal brain cooling in animal models
• Steps toward practical cooling-based therapies for human epilepsies
• Establish a place for focal cooling within the NINDS Epilepsy Research Benchmarks
Focal cooling and NINDS Epilepsy Benchmarks

Benchmarks Area I - Prevent epilepsy and its progression

D) Identify approaches to prevent epilepsy or its progression
   2) Identify interventions that prevent, interrupt or reverse the epileptogenic process

Benchmarks Area II: Develop new therapeutic strategies and optimize current approaches to cure epilepsy

C) Optimize existing therapies and develop new therapies and technologies for curing epilepsy
   2) Develop new approaches (e.g. gene therapy, brain stimulation, cellular therapy, pharmacotherapy) for targeted therapies

• Benchmarks Area III: Prevent, limit, and reverse the co-morbidities associated with epilepsy and its treatment
Focal Cooling for Epilepsy
Temperature : Seizure relationship

• Hippocrates:
  – “the excess of phlegm cuts off the psychic pneuma so that it does not quite fill the nerves, and that this causes the spasms of epilepsy and cessation of breathing in the seizure....a hot head from exposure to the sun or to fire, a sudden rigor, and fear or crying, could cause the phlegm in the brain to melt, thus precipitating an epileptic attack.”

  On The Sacred Disease, 400 B.C.

• Febrile seizures
• Systemic cooling for seizures
Systemic cooling controls intractable SE

4 adults, 31-35 ºC
(CoolGard 3000 Thermal Regulation System, Alsius Corp)

Hypothermia for Refractory Status Epilepticus

Jesse J. Corry · Rajat Dhar · Theresa Murphy · Michael N. Diringer

Neurocrit Care, 2008

5 children, 32-35 ºC
(Arctic Sun, Bard Medical)

Hypothermia for pediatric refractory status epilepticus

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Epilepsia, 2013
Focal brain cooling: Historical perspectives

Temple Fay* investigated local/systemic cooling for trauma, tumors, pain in Philadelphia and Boston (1938 to 1959)

- Constraints on mobility
- Technology limitations

Invasive cooling for seizures

25 patients with refractory motor seizures

- General anesthesia
- Enclosed cooling chamber to 29°C core temp
- Burr holes and iced saline irrigation (subarachnoid and intra-ventricular)
- One year follow-up:
  - 11/15 reduced sz freq
  - 4 seizure free (27% Engel I)
  - 7 improved (47% Engel II-III)
  - 4 unchanged (27% Engel IV)

General and local hypothermia of the brain in the treatment of intractable epilepsy

K. Šourek, M.D., and V. Trávníček, M.D.
Neurosurgical Clinic, Charles University, Prague, Czechoslovakia
Focal Cooling Suppresses Spontaneous Epileptiform Activity without Changing the Cortical Motor Threshold

*Kameel M. Karkar, *Paul A. Garcia, *Lisa M. Bateman, †Matthew D. Smyth, †Nicholas M. Barbaro, and †Mitchel Berger

Departments of *Neurology and †Neurological Surgery, University of California, San Francisco, San Francisco, California, U.S.A.

Epilepsia, 2002

Motor threshold 4 mA
Surface iced saline irrigation: 4°C
Focal cooling implant concept: Peltier device

Semiconductor with properties such that one side cools while the other side warms when current applied: Temperature correlates with current

Rothman and Smyth, Epilepsy Behav 2005
Challenges to implementation:

- What temperatures are necessary...
  ...to abolish seizures?
  ...to suppress neurologic function?
  ...to prevent epileptogenesis?
- Method of cooling delivery?
- Heat dissipation?
- Seizure detection?
- Neurotoxicity?
- Surface...depth...sulci?
Acute evoked seizures in rodents

- Inexpensive, reproducible
- Well-characterized seizure models in rats
- Permits rapid assessment of seizure suppression

2000-2005:

- \textit{In vitro} slice (4-AP)
- \textit{In vivo} anesthetized (4-AP)
- awake freely moving (kindled)
Evoked seizure models require surface cooling in the range of 22-25°C.
Transcortical Cooling Inhibits Hippocampal-kindled Seizures in the Rat

*Justin M. Burton, *Gregory A. Peebles, †Devin K. Binder, ‡Steven M. Rothman, and *Matthew D. Smyth  

Epilepsia, 2005
Suppression of KA-induced seizures by direct hippocampal cooling

Temperature threshold to abolish seizures: 20-25°C
Temperature threshold to inhibit normal function: 10-15°C

Problem: In conventional seizure models, substantial cooling required for incomplete control of evoked seizures.

Would chronic spontaneous (i.e. epileptic) seizures be more sensitive to cooling?
Fluid Percussion Injury: a model of contusive closed head injury and spontaneous recurrent seizures

- D’Ambrosio et al. Post-traumatic epilepsy following fluid percussion injury in the rat. Brain, 2004
- D’Ambrosio et al. Progression from frontal-parietal to mesial-temporal epilepsy after fluid percussion injury in the rat. Brain, 2005
Rostral parasagittal fluid percussion injury (rpFPI): a rat PTE model

- Clinically relevant model of contusive closed head injury-
  TBI is epileptogenic in humans

- Reproduces many pathophysiological features of human PTE
  Focal onset, latent period and evolution, pharmacoresistant,
  chronic spontaneous events similar to CPS

- Rapid epileptogenesis (weeks)

- High incidence of PTE (>90%)

- High seizure frequency

- Predictable neocortical focus

Prototype cooling device to be implanted over region of brain exposed to FPI for active water-cooling

Prototype coolant circulation switch with TTL trigger for automated coolant circulation

Discovery of passive mild cooling effect

Mild Passive Focal Cooling Prevents Epileptic Seizures After Head Injury in Rats

Raimondo D’Ambrosio, PhD, Clifford L. Eastman, PhD, Felix Darvas, PhD, Jason S. Fender, BS, Derek R. Verley, BS, Federico M. Farin, MD, Hui-Wen Wilkerson, BS, Nancy R. Temkin, PhD, John W. Miller, MD, PhD, Jeffrey Ojemann, MD, Steven M. Rothman, MD, and Matthew D. Smyth, MD

- FPI and implantation of cooling device and EEG electrodes
- Baseline seizure frequency analysis (EEG-Video)
- No seizures!

D’Ambrosio et al., Annals of Neurology, 2013
Mild focal cooling of the rat brain after rostral parasagittal FPI: Headset Redesign

Assembly of focal cooling headsets

ECoG montage

cooling performance

D'Ambrosio et al., Annals of Neurology, 2013
Steady state dose response of CSRS to mild cooling 0.5 to 2.0 °C (blinded and randomized studies)

D’Ambrosio et al., Annals of Neurology, 2013
Steady state dose response of CSRS to mild cooling (blinded and randomized studies)

Continuous passive cooling 0.5 to 2.0 ºC

D’Ambrosio et al., Annals of Neurology, 2013
2°C focal cooling prevents epileptic seizures after head injury

Anti-epileptogenesis (blind and randomized studies)

Weeks after injury

Randomization + headset

Cooling

5 weeks of 2°C focal cooling
Starting 72 hours after injury

Aggregate seizure burden (seizure frequency and duration) reduced > 99% in this PTE model

D’Ambrosio et al., Annals of Neurology, 2013

Rare seizures shorter, > 15 sec abolished
Focal cooling confirms the neocortical origin of rpFPI epilepsy

D’Ambrosio et al., Annals of Neurology, 2013
Lack of neurotoxicity

D’Ambrosio et al., Annals of Neurology, 2013
Human Subdural/epidural cooling grid for neocortical focus

Alternative to resection of eloquent cortex?
Subdural/epidural Cooling Grid
Target: neocortical

Alternative to resection of eloquent cortex?
8 x 8 Thermoelectric Grid for Cooling Focal Neocortical Diseases

- Single thermocouple
- Flexible heat pipe to withdraw heat
- Individual wires terminating in other pole of power supply
- To one pole of DC power supply for thermoelectric modules

Cold surface of thermocouple module

Monopolar EEG lead

Power supply for Peltier

Thermocouple connection
Depth cooling implantable device
Target: mesial temporal

Heat sink
Peltier
Heat pipe
insulation
Recording electrodes (4)
Wires for connecting electrodes and Peltier to current

U.S. Patent Application Serial No. 12/164,857
Conclusions

• Cooling by 0.5 to 2°C inhibited the onset of epileptic seizures in a dose-dependent fashion

• Cooling by 2°C for 5.5 weeks beginning 3 days after injury virtually abolished ictal activity

• This effect persisted until at least 10 weeks after cooling cessation

• Rebound seizures after rewarming were not observed

• Focal cooling has anti-convulsant and anti-epileptogenic properties

• No evidence of induced pathology, inflammation, or alterations in neuronal activity were observed

• Clinical implementation far more practical with small ΔT
  – Both active cooling or passive heat dissipation devices may be effective
Team Members and Acknowledgments

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- Raimondo D’ Ambrosio
- John Miller

Mercy Hospital, St. Louis MO
- Steven Rothman

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