



COLLEGE OF ENGINEERING
UNIVERSITY OF WISCONSIN-MADISON

DEPARTMENT OF BIOMEDICAL ENGINEERING

A Device for Brain Cooling in Mice

Jay Sekhon--Leader
Jon Seaton – Communicator
David Leinweber – BSAC
Mark Reagan – BWIG

Client: Giulio Tononi Ph.D./M.D.
Ugo Faraguna Ph.D./M.D.

Advisor: Mitch Tyler

March 11, 2009

Table of Contents

Background	3
Client Requirements	4
Project Aims	5
Similar Devices	6
Product Uniqueness	7
Design Alternatives	7
<i>Peltier Cell</i>	7
<i>Vortex Tube</i>	8
<i>Liquid-Cooling</i>	9
<i>Phase-Change Cooling</i>	10
Design Matrix	11
Thermodynamics	12
Testing	13
Future Work	14
Appendix A (PDS)	15
Appendix B (Expenses)	18
References	20

Background

The function of sleep remains one of the greatest unsolved mysteries in modern science. A multitude of theories have been proposed regarding the necessity of sleep, but none have been substantively established.

Sleep is known to be an essential process of life, taking up almost 1/3 of the average human's lifetime. Furthermore, it is such a necessity that deprivation has been known to cause health problems in rats, leading up to death (Everson 1995). Additionally, the effects of sleep have been studied on a variety of life factors. Retaining homeostasis is a commonly accepted view, since studies have shown that lack of sleep hampers healthy metabolic activity and immune system response (Zager 2007). Furthermore, sleep has been linked to proper memory function—lack of sleep has been shown to correlate with cognitive impairment, decreasing by as much as 38% in comparison to a control (Turner 2007). However, these functions all provide effects of sleep; they do not examine the purpose of it.

A hypothesis has been proposed by Dr. Giulio Tononi that sleep is used for synaptic downsizing. Specifically, he states that “The synaptic homeostasis hypothesis claims that plastic processes during wakefulness result in a net increase in synaptic strength in many brain circuits; during sleep, synaptic strength is globally downscaled to a baseline level that is energetically sustainable and beneficial for memory and performance” (Tononi 2005). The client has started an experiment to test this hypothesis, using 2-photon microscopy to image synaptic activity in the brain in awake and sleeping mice. The client has proposed an additional experiment based upon the neural activity hypothesis.

The rationale behind the second experiment lies in the logic assumed by an increase in synaptic strength. If the hypothesis is correct, then wakefulness with a decreased level of synaptic activity will produce a longer time between sleep/wake cycles. Additionally, it has been shown that cooling of brain tissue will reduce synaptic activity (Benita & Conde 1972, Waleszczyk 2005). With this line of reasoning, the client wishes to selectively cool a region of the brain that is responsible for modulating the sleep/wake cycle. By doing so, he believes that he will be able to silence the synaptic activity, affecting the sleep cycle.

In order to carry out this new experiment, the client would like a device capable of cooling a 3mm hemispherical region of a mouse's brain. The device must be able to cool the tissue enough to silence neural activity, but not so much that tissue damage occurs. Furthermore, the device needs to allow the acquisition of an accurate EEG signal in order to confirm that synaptic activity has been suppressed.

Client Requirements

At the beginning of the semester, our client, Dr. Ugo Faraguna, provided a specific set of requirements. In order to correctly build our prototype, it is imperative that we follow these requirements. Most importantly, we must cool a 3 mm region in the brain to approximately 20°C. As the device reaches the desired cooling temperature, it must not harm the brain cells in any way. Although the client believes it is impossible to completely avoid killing a few brain cells, it would be ideal to find a temperature that will not damage the tissue. The device should be able to cool down the area efficiently—

meaning it should only take about 30 to 60 minutes to reach the ideal temperature. After the device has cooled the brain region to the desired temperature, the client will run various tests. As such, the temperature should be constant during these tests ($\pm 0.5^{\circ}\text{C}$) and should be able to last for three to six hours. As mentioned previously, it is important that the device does not cause any interference to the EEG signal. If the device does produce interference, it would defeat the purpose of the client's experiment which is predicated on the suppression of EEG signals. Another important piece of criteria is the mobility and ease of use of the device. Ideally, the device should be able to fit on a cart so it is capable of being taken from room to room if it needs to be used in more than one experiment. It should also be easy to use, so that the temperature can be controlled by the client in order to successfully carry out the desired experiments.

Project Aims

The main goal of the device is to cool down a 3mm hemispheric region in a mouse's brain. The area should be cooled to approximately 20°C , which is the first priority of the device. The second priority of the device is to make sure the device does not interfere with obtaining an EEG signal. This is critical because if there is noise in the EEG signal, it will appear as if there is activity in the brain. The third priority involves temperature measurement. Once the previous two aims are complete, a temperature gauge should be placed at the site of the cooling to allow the client to obtain the tissue temperature. Realistically, the first two aims should be accomplished this semester.

Similar Devices

Similar devices have been built in multiple research labs. The most similar apparatus was constructed at Yamaguchi University School of Medicine in Ube, Japan. The reason for the construction was quite different than in the case of our project, and focused on creating a device to treat patients with epilepsy. They hypothesized they could decrease the effects of seizures by cooling the brain with a Peltier chip. This hypothesis was tested on the brains of rats. In this experiment, the Peltier cell was used to cool the brain tissue between 14°C and 23°C. According to the article, the researchers were satisfied with the Peltier device. A very important component in their construction was a heat sink because the hot side of the Peltier device reached temperatures over 60°C and was not able to function for a period of time. A schematic of the device is shown below:

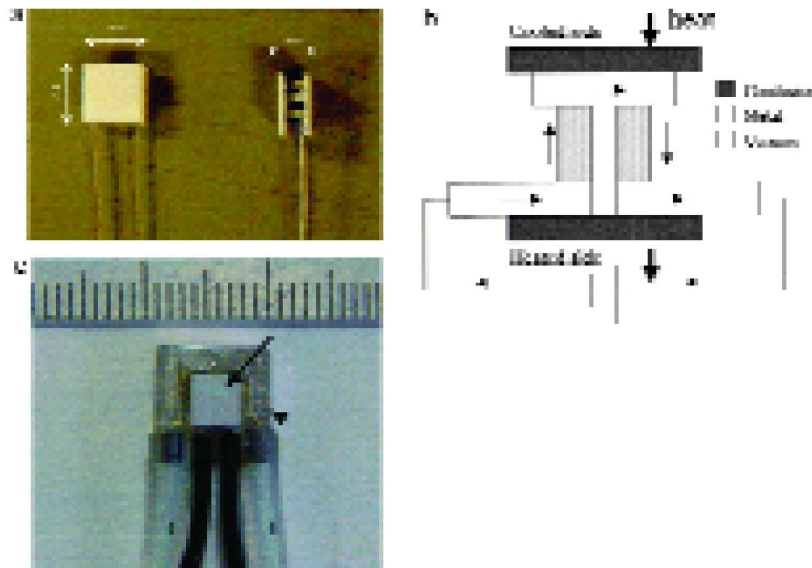


Figure 1 (Imoto 2006): Photograph of the thermoelectric device (Peltier chip). b: Diagram demonstrating the Peltier chip. Two conductors are connected in parallel. When the electrical current is passed between them, heat is transferred from one side, which then cools, to the other, which then heats (**bold arrows**). *Arrows* depict the flow of electrons c: Photograph of the newly devised cooling system. *Arrow* depicts the Peltier chip; *arrowhead* indicates the heat sink made of aluminum containing a fluid channel (*asterisk*).

Product Uniqueness

Our product will strive to create a more efficient cooling device by trying to obtain a more consistent temperature gradient. In essence, however, the device is accomplishing the same task mentioned above.

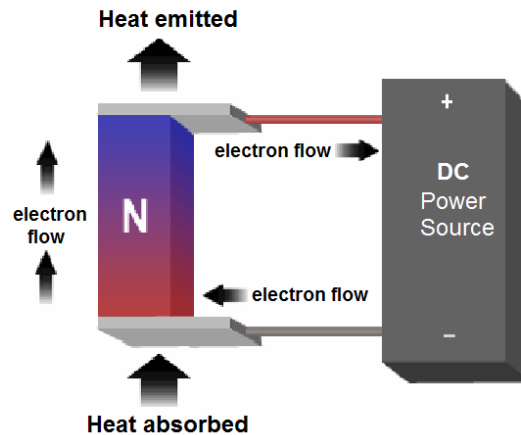
Design Alternatives

Peltier Cell

A Peltier cell is a circuit component that transfers heat in the direction of electron flow, as in Figure 2. The cell itself consists of two plates and a solid compound between the plates that allows heat transfer against the thermal gradient—creating a “cold” side and a “hot” side. The energy transfer in this manner is changed by current—higher currents create a greater heat transfer. The “hot” side of the cell can overheat and cause damage to the circuit, however, and in order for the cell to properly function continuously, the heat needs to be dissipated in another fashion.

The Peltier cell has been used by the client before, without a heat sink on the hot side. The client said that the cell worked marvelously for a short while, until damage to the component occurred due to excessive heat concentration. This design, however, is beneficial due to its accuracy, adjustability, biocompatibility, and size. Accurate temperature measurements are obtainable by calculation based upon the cell’s specifications and the voltage that is passed through. Changing the temperature is likewise simple—current changes across the cell will produce a temperature change.

Furthermore, it is highly biocompatible, since it makes no noise, and it can be smaller than 3mm, making it the ideal size for this application.



Adapted from: http://www.marlow.com/TechnicalInfo/images/faq_fig1.gif

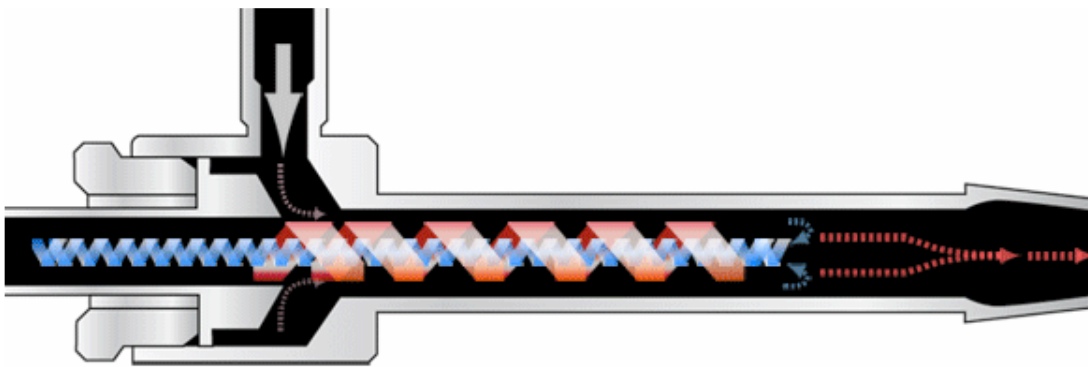
Figure 2. Diagram of Peltier Cell.

Vortex Tube

In this method, air is forced through a tube where it is rotated at nearly 1,000,000 rpm to separate air particles based on their kinetic energy. In this way, hotter air particles are forced toward the outside and cooler air particles are squeezed inside of the tube. Once the particles reach the right side of the tube as seen in Figure 3, only the hot air is allowed to escape. The cold air is then further compressed within this outer warm air cycle, before being released through the left side of the tube in Figure 3. This results in even greater cooling based on the ideal gas law, since the air expands in volume upon exit. This process can produce temperature differentials of up to 150°C: cold air at -40°C and hot air at 110°C.

The benefits of this method include its accuracy, adjustability, and its complete mechanical operation. The vortex tube requires no electrical components or movement of

dense fluids, making it the most compatible with EEG measurements. Also, the device can be easily adjusted to emit the correct temperature air simply by changing the input pressure. However, the device can have loud airflow, which could prevent the mouse from being able to sleep.



Source: http://www.process-controls.com/techsales/Nex_Flow/vortex_tube.htm

Figure 3. The inner workings of a vortex tube during operation. The red lines represent warm air and the blue lines represent cold air.

Liquid Cooling

In this method, liquid is cooled to the correct temperature and moved through a heat block over the mouse's brain. In the heat block, the liquid absorbs heat from the mouse, and the warmed liquid is then moved through a radiator and cooled with a fan. This cooled liquid is then cycled back through the heat block. This process would continue until the brain has reached the desired temperature.

One of the major benefits of this method would be its relatively low cost and simple construction. It is also relatively efficient at removing heat and easy to operate. However, some liquid coolants are highly toxic if absorbed into the body and it can be difficult to adjust the temperature of the liquid to an accurate value and hold it for up to 6 hours.

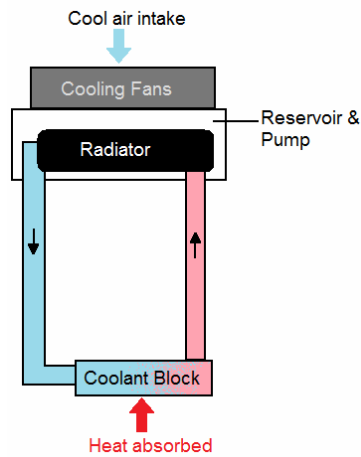


Figure 4. Liquid cooling method diagram.

Phase-Change Cooling

Similar to the liquid cooling method, phase-change cooling instead involves the conversion of a gas to a liquid instead of just using a liquid. Compressing a gas and moving it through a radiator to remove heat energy creates this liquid. After this heat is removed the compound is depressurized, which causes a decrease in temperature, forming a liquid. The liquid is then cycled as described in the liquid cooling method to cool the mouse's brain tissue.

The major benefit of this method over the liquid cooling method is the ability to reach much lower temperatures, potentially even below -50°C . However, low temperatures such as this would create a greater temperature gradient between the heat block and brain tissue, possible leading to damage of the upper layer of tissue and cell death.

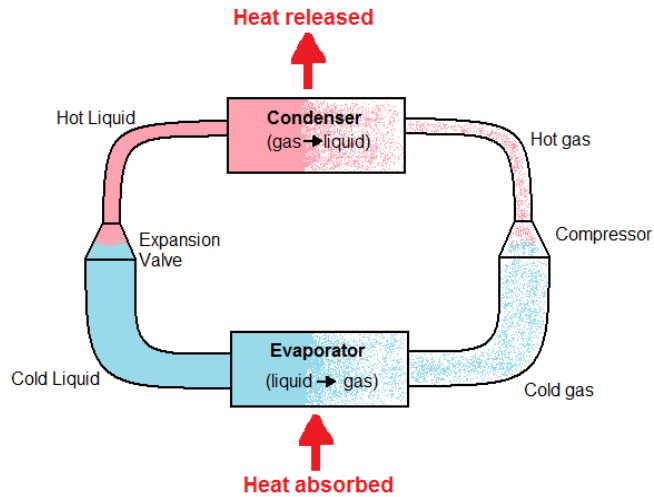


Figure 5. Phase-change cooling method.

Design Matrix

From the previous four design alternatives, the following design matrix was developed (Figure 6). The categories accounted for include accuracy of the cooling method; compatibility with EEG signals; compatibility with the mouse; size of the area that could be cooled; the temperature gradient between the device and the brain tissue; the adjustability of temperature; ease of operation; cost; durability; and efficiency. Cooling accuracy, EEG compatibility, and mouse compatibility were determined to have the greatest importance in design of the device. After evaluation, it was determined that the Peltier cell would be ideal followed by the vortex tube, liquid cooling, and phase-change cooling.

	Weight	Peltier Cell	Vortex Tube	Liquid Cooling	Phase-Change Cooling
Cooling Accuracy	15	13	10	7	7
EEG Compatibility	15	7	13	10	10
Mouse Compatibility	15	13	7	10	10
Cooling Area	10	9	7	5	5
Temperature Gradient	10	9	8	7	3
Temperature Adjustment	10	9	7	3	3
Ease of Operation	10	9	5	7	7
Cost	5	4	3	5	3
Durability	5	3	5	4	4
Efficiency	5	4	3	4	5
TOTAL	100	80	68	62	57

Figure 6: Design Matrix

Thermodynamics

Because the project has a large amount to do with heating and cooling, it is imperative to discuss thermodynamics. In order to understand how much energy is needed to cool the desired area in the brain, Newton's law of cooling must be used. Newton's law of cooling is the following:

$$Q = mC_p\Delta T$$

Where Q is heat, m is mass, C_p is the specific heat capacity of the substance, and ΔT is the change in temperature. In order to find the energy needed to cool the 3mm space in the brain, the parameter values are necessary. The ambient body temperature of a mouse is 39°C (Imoto 2006). As previously stated, the goal of the project is to cool the hemisphere in the brain by approximately 20°C . Therefore, ΔT is the ambient body temperature of the mouse minus the intended temperature, which in this case is:

$$\Delta T = T_1 - T_2 = 39^\circ\text{C} - 20^\circ\text{C} = 19^\circ\text{C}$$

The mass was calculated via density. The volume of the target region is a hemisphere and was thus calculated using a 2 to 3 mm diameter. The density of brain tissue is 1.071 g/cm^3 . These measurements were plugged into the following equation to find the mass of the area being cooled.

$$\text{mass} = \text{volume} \times \text{density} = \frac{1}{2} \left(\frac{4}{3} \pi r^3 \right) \times \rho = \frac{1}{2} \left(\frac{4}{3} \pi (.15)^3 \right) \times (1.071)$$

Using these measurements the mass of the area to be cooled is 7.57 mg.

The specific heat of tissue is $3.6 \text{ J} \cdot \text{g}^{-1} \cdot \text{m}^{-1}$ (Elwassif 2006), so the energy to liberate is:

$$Q = (0.00757)(3.6)(19) = 0.518 \text{ J}$$

Using the parameters previously discussed and plugging them into the Newton's law of cooling equation, it was found that 0.518 J need to be liberated to cool the area of the brain to 20°C .

Testing

Because the project has been focused more on design alternatives until this point, we have done little formal testing. Even though we have not done any formal testing, we did perform some informal tests, focusing on the vortex tube. Our preliminary research indicated the vortex tube would be relatively simple to work with at low air pressures. After testing the vortex tube with a low air pressure (5-40 psi) that we thought would be sufficient for the amount of cooling needed, we learned that this pressure was insufficient for the proper function of the vortex tube. Instead, we needed a greater pressure. Also during this test, we discovered that it would be challenging to keep the air compressor at a constant pressure for an extended amount of time. This would almost defeat the entire

ease of use quality that we thought was a key characteristic of the vortex tube. After completing this preliminary testing, we realized that the vortex tube may not be the optimal cooling device for our purposes which caused us to devise a backup plan.

Future Work

Moving forward, device fabrication is the main objective. Before the device is actually built, a few formal tests will be run on the components to make sure that they will perform as expected. Tests will be similar to that described above with the vortex tube, although they will be more formal and rely on quantitative values, rather than simple proof-of-concept. More specifically, testing will be done regarding the heat sink for the Peltier cell. As seen in the design matrix, the Peltier cell will be the key device in the project. The client has used a Peltier cell in previous studies and found that he needs a heat sink to cool the hot side of the cell, otherwise circuit failure and component damage occurs. In order to curb this phenomenon, a heat sink will be designed for the Peltier cell. This can be done using any of the other three design alternatives (vortex tube, liquid cooling, or phase-change cooling), but each of these options must be tested to determine the most efficient performance as a heat sink.

After the device is built, tests will be run in a simulated environment using agarose as a substitute for the brain tissue. After these tests are successful and approved by the client, the device will be complete.

APPENDIX A

Project Design Specifications

PRODUCT DESIGN SPECIFICATIONS

Date: February 5th, 2009

Project Title: #28 Brain Cooling Device

Team Members:

Jay Sekhon – Team Leader
David Leinweber – BSAC
Jon Seaton – Communicator
Mark Reagan – BWIG

Client:

Ugo Faraguna
UW Psychiatric Institute
Phone: 263-7753 □
Email: faraguna@wisc.edu

Function:

Sleep is homeostatically regulated; the more we are awake, the more intensely we need to sleep. However, while this is a common experience, the actual mechanism behind the regulation of sleep is poorly understood. In order to further our understanding of this phenomenon, *in vivo* imaging of genetically engineered YFP fluorescent mice will be performed on brain synapses. It is believed that comparing the activities of neurons while awake and asleep could conclude that sleep is regulated by these metabolic changes. In order to rule out other possibilities such as simply kinetic regulation, neurons in a specific area of the brain must be silenced for a span of time and its affect on sleep analyzed. In order to do this, a miniature device must be constructed to cool the temperature in an area of the brain of a mouse to a low enough temperature to silence neural activity while preventing necrosis.

Client Requirements:

- Create a device to silence neurons in an area of 1-3 mm in diameter by cooling.
- The device needs to have a way of recording the temperature gradient that is formed in the 1-3 mm area
- The device must not interfere with the EEG signals.
- The device must be able to cool a mouse's brain and thus must be very small.
- The device must cool a mouse's brain (38-39°C) to as low as 19-20°C
- The device must be able to cool the tissue to a selected temperature in the range of 19-25°C and be able to keep the tissue at the selected temperature for up to 6 hours. Thus it must have variable temperature controls.
- Materials used should be durable with little need for maintenance.

- The device must be completed and functional by the end of the semester
- The budget for the device and prototypes is \$1000.

Physical and Operational Characteristics

- *Performance requirements:* The device will be used in multiple studies and must be continuously operational for 1-6hrs.
- *Safety:* The device must be biocompatible, nontoxic, and easily cleaned to reduce the possibility of spreading infection amongst animals.
- *Accuracy and Reliability:* The device must be able to record, adjust, and maintain to temperatures within $\pm 0.5^{\circ}\text{C}$. The device will be used continuously for up to 6hrs.
- *Shelf Life:* The device will be stored at standard temperature and pressure in non-condensing humidity.
- *Operating Environment:* The device will be operated at standard temperature and pressure in non-condensing humidity, however temperatures as low as 19°C will be produced. The device will be in direct contact with brain fluids and tissue during operation.
- *Ergonomics:* The device will rest on the brain of a mouse and must not induce any pain or unnecessary stress.
- *Size:* The device must cool an area of 1-3mm, but other working components may be much larger. The device must be portable by one human with a cart.
- *Weight:* The device must weigh within the limits of a human's ability to move from room to room.
- *Materials:* Must be biocompatible and nontoxic with direct contact to brain tissue and bodily fluids. Materials that conduct electricity are discouraged.
- *Life in Service:* 1-2 years.

Production Characteristics

- *Quantity:* One unit
- *Time of Manufacture:* Within Semester
- *Target Product Cost:* <\$1000

Miscellaneous

- *Standards and Specifications:* Device will need to be approved by the IACUC (Institutional Animal Care and Use Committee)
- *Customer:* The customer has attempted using a small Peltier cooling device, but had difficulty with creating an adequate heat sink. Also, a rough liquid cooled device had been used, but it produced noise in the EEG signal.

APPENDIX B

Expenses

MID-SEMESTER REPORT

March 11, 2009

Expense Sheet			
Product	Date	Where	Cost
Vortex Tube	2/12	lcoolsmart.com	\$200.00
Valves	2/19	Home Depot	\$45.00
Air Compressor	8/6	Home Depot	\$90.00
		Total	\$335.00

References

- Bakken, H. E., et al. "A Device for Cooling Localized Regions of Human Cerebral Cortex. Technical Note." Journal of neurosurgery 99.3 (2003): 604-8.
- Battista, A. F. "Effect of Cold on Cortical Potentials in the Cat." Experimental neurology 19.2 (1967): 140-55.
- Benita, M., and H. Conde. "Effects of Local Cooling upon Conduction and Synaptic Transmission." Brain research 36.1 (1972): 133-51.
- Burton, J. M., et al. "Transcortical Cooling Inhibits Hippocampal-Kindled Seizures in the Rat." Epilepsia 46.12 (2005): 1881-7.
- Cespuglio, R., et al. "Alterations in the Sleep-Waking Cycle Induced by Cooling of the Locus Coeruleus Area." Electroencephalography and clinical neurophysiology 54.5 (1982): 570-8.
- Chafee, M. V., and P. S. Goldman-Rakic. "Inactivation of Parietal and Prefrontal Cortex Reveals Interdependence of Neural Activity during Memory-Guided Saccades." Journal of neurophysiology 83.3 (2000): 1550-66.
- Clarey, J. C., R. Tweedale, and M. B. Calford. "Interhemispheric Modulation of Somatosensory Receptive Fields: Evidence for Plasticity in Primary Somatosensory Cortex." Cerebral cortex (New York, N.Y.: 1991) 6.2 (1996): 196-206.
- Clark, D. L., and F. Colbourne. "A Simple Method to Induce Focal Brain Hypothermia in Rats." Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 27.1 (2007): 115-22.
- Elwassif MM, Kong Q, Vasquez M and Bikson M. "Bio-heat transfer model of deep brain stimulation-induced temperature changes." Journal of neural engineering 3(4) (2006): 306-15.
- Everson, C. A. (1995). "Functional consequences of sustained sleep deprivation in the rat." *Behav Brain Res*, 69(1-2), 43-54.
- Fingas, M., D. L. Clark, and F. Colbourne. "The Effects of Selective Brain Hypothermia on Intracerebral Hemorrhage in Rats." Experimental neurology 208.2 (2007): 277-84.

- Imoto, H., et al. "Use of a Peltier Chip with a Newly Devised Local Brain-Cooling System for Neocortical Seizures in the Rat. Technical Note." Journal of neurosurgery 104.1 (2006): 150-6.
- Long, M. A., and M. S. Fee. "Using Temperature to Analyse Temporal Dynamics in the Songbird Motor Pathway." Nature 456.7219 (2008): 189-94.
- McCulloch, J., et al. "Local Cerebral Glucose Utilization in Hypothermic and Hyperthermic Rats." Journal of neurochemistry 39.1 (1982): 255-8.
- Rothman, S., and X. F. Yang. "Local Cooling: A Therapy for Intractable Neocortical Epilepsy." Epilepsy currents / American Epilepsy Society 3.5 (2003): 153-6.
- Tanaka, N., et al. "Effective Suppression of Hippocampal Seizures in Rats by Direct Hippocampal Cooling with a Peltier Chip." Journal of neurosurgery 108.4 (2008): 791-7.
- Tononi, Giulio. (2005) "Research Overview—The Center for Sleep and Consciousness." http://tononi.psychiatry.wisc.edu/research_overview.html
- Turner, T. H., Drummond, S. P. A., Salamat, J. S., & Brown, G. G. (2007). "Effects of 42 hr sleep deprivation on component processes of verbal working memory." *Neuropsychology*, 21, 787-795
- Waleszczyk, W. J., M. Bekisz, and A. Wrobel. "Cortical Modulation of Neuronal Activity in the Cat's Lateral Geniculate and Perigeniculate Nuclei." Experimental neurology 196.1 (2005): 54-72.
- Yang, X. F., and S. M. Rothman. "Focal Cooling Rapidly Terminates Experimental Neocortical Seizures." Annals of Neurology 49.6 (2001): 721-6.
- Zager, A., Andersen, M. L., Ruiz, F. S., Antunes, I. B., & Tufik, S. (2007). "Effects of acute and chronic sleep loss on immune modulation of rats." *Regulatory, Integrative and Comparative Physiology*, 293, R504-R509