



Charité NeuroScience

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heat

or

COLD

what's good
for the brain?

Page 3 - 14 FOCUS

Hyperthermia in Brain Injuries
 Hyperthermia in Neuroleptic Malignant Syndrome
 Hyperthermia Impairs Memory Functions
 Fever: Good or Bad?
 Hyperthermia, Heat Shock Proteins and Immunity
 Hypothermia in Wernicke-Korsakoff Syndrome
 When Your Eyes Say it ... Ophthalmic Injuries
 Hyperthermia : The Coolest Treatment for Stroke
 Hyperthermia for Neuroprotection after Cardiac Arrest
 Cognitive Outcomes after Hypothermia Therapy in Cardiac Arrest Patients
 E-Learning "Cardiac Arrest, Hypothermia and Resuscitation Science"
 Cooling - Hope after Neonatal Hypoxic-Ischemic Encephalopathy
 Arnaldur Indriðason - Hypothermia
 TRP Channels - Our Bodies' Thermometers
 Hypo-/Hyperthermia-Based Clinical Trials
 Perception Leads Reality - The Effect of Temperature on Perception

Page 13 Whatever Happened To ...

A Conversation with Guido Guenther

Page 14 A Taste of Home & Check This Out

Motor Neuron Disease Documentary

Page 16 Conference Report & Course Watch

The Most Specialized Community for Blood-Brain Barrier
 5th G-Node Winter Course in Neural Data Analysis

Page 17 Open Positions & Dr. Harebrained

Page 18 Crossword

Page 20 News in Brief & WhazzUp?

Best Regards to All of You!**Ice Ice Baby!**

This summer has been nice and hot and we have all had moments where we would do bad things for some vanilla icecream, haven't we? Have you ever worried if temperature – too hot or too cold – affects your brain? Can a 'fried' or 'frozen' brain ever be a good thing?

Given the heat wave, our editorial team has been working hard to tackle these questions and we've got some interesting conclusions for you. Read on for answers on how hyperthermia impairs memory function, how temperature is measured in the body, which diseases are caused or affected by hypo- or hyperthermia and how cooling therapies can be applied to treat brain diseases.

Apart from the burning articles of this issue's theme, read a success story of becoming a Neurology professor: Meet Guido Guenther, an MSc Medical Neurosciences graduate, el profesor universitario en México. And while we're on the topic of México, give your taste buds a treat and visit some of our reviewed Taste of Home restaurants. Tasty, spicy, and without a doubt, hot Mexican food.

Do not miss the conference report on the most specialized community for blood-brain barrier, a winter school report on Neural Data Analysis, and the Motor Neuron Disease Documentary. Sounds appetizing so far, but what has Dr. Harebrained come up with to answer the question: Why is it again that blood (hemorrhage) is toxic for the brain? Read the full story.

The editorial team is also a hotbed of change at the moment: We are very happy for Gina Eom, a long-lasting member of our editorial team, who has submitted her PhD thesis. However, this also means that she has to leave us. Inês Laginha, who is also at the end of her PhD, has to leave us as well. We wish them the very best for their futures and hope to hear about their achievements soon. Fortunately, we welcome two new writers to our editorial team: Ahmed Khalil and Filip Morys. Ahmed will also be part of the proofreading team.

Last but not least, this issue's winner of the contest is Tian Zhang who contributed two articles to this issue: "The Role of Hyperthermia in Brain Injuries" and a conference report about "The Most Specialized Community for Blood Brain Barrier". A Medical Neurosciences messenger bag has now found a new shoulder.

What drives you 'insane'? What do you want to have light shed on? Any intriguing topics/ideas should be submitted to cns-newsletter@charite.de. Any questions or comments about this or any other issue? Just let us know!

Enjoy reading!

- Marietta, Editor-in-Chief

Cover: Julia Rummel

With great interest I read Tian Zhang's article in the June 2013 CNSNewsletter (p.5), which describes the 'increasing perception of being above average'. While I personally doubt that there is robust evidence to state that unfounded overconfidence in one's own performance or skills is increasing, the phenomenon is well studied and even carries an eponym: The Kruger-Dunning effect, which is a 'cognitive bias in which unskilled individuals suffer from illusory superiority, mistakenly rating their ability much higher than average (<http://bit.ly/cMhwUo>). I recommend the excellent article 'Why the Unskilled Are Unaware: Further Explorations of (Absent) Self-Insight Among the Incompetent' by Ehrlinger et al. (Organ Behav Hum Decis Process. 2008 January 1; 105(1): 98-121. <http://1.usa.gov/KLLfwI>) for those of you further interested in this practically relevant phenomenon. It investigates the logical impossibility that the majority is convinced that they are better than average. The article tests (and confirms) the hypothesis that 'poor performers lack insight into their shortcomings even in real world settings and when given incentives to be accurate'. As a practical exercise I might recommend self-rating our own performance :-)

Ulrich Dirnagl, Center for Stroke Research Berlin

The Role of Hyperthermia in Brain Injuries

By Tian Zhang, PhD Student Medical Neurosciences, AG Clinical Neuroscience

Why is it so important to keep the brain cooled down following brain injuries? Although the brain represents only 2-3% of our body weight, it uses up to 20% and 25% of the body's total consumption of oxygen and glucose, respectively. In contrast to other organs, such as muscle, the heat produced by cerebral metabolism cannot easily be dispersed because the brain is protected by the skull. Therefore, overwhelming evidence supports the notion that moderate elevation of brain temperature frequently seen in brain-injured patients may markedly worsen outcome. Regardless of the underlying cause, hyperthermia increases metabolic rate, glutamate accumulation, and neutrophil activity to levels higher than normothermic brain-injured patients. This may synergistically compromise the injured brain and exacerbate neuronal damage.

Pathophysiology of Hyperthermia

Hyperthermia is a rise in body temperature above the norm [1]. By definition, all fevers are hyperthermia, but not all hyperthermia responses are fever. Hyperthermia in brain injury can be secondary to systemic fever, possibly due to infection [2], injury in the thermoregulatory center, or a reflection of a state of sterile inflammation generated by local metabolic alteration and neuroimmune interactions [3].

In traumatic brain injury (TBI), post-traumatic hyperthermia is a noninfectious elevation in body temperature and is also known as neurogenic fever. It results from traumatic injury to the thermoregulatory hypothalamus and a subsequent disruption in the hypothalamic 'set point' temperature [4]. Increased temperature after brain trauma has been associated with increased acute phase responses including cytokine activity, white cell accumulation, vascular permeability, and axonal damage in experimental models of TBI [5]. Moreover, posttraumatic release of proinflammatory cytokines such as IL-1 and tumor necrosis factor alpha (TNF- α) from myeloid cells at the site may cause the release of IL-6 (the principal endogenous pyrogen), Prostaglandin E, and reactive oxygen species [6]. They may act as exogenous stimuli to further trigger an acute febrile response following TBI. Besides,

glutamate released from injured cells can result in cytotoxicity. When hyperthermia is present, an add-on effect can be expected as glutamatergic pathways have been recently implicated in experimental pyrogenic fever production [7]. Nitric oxide (NO) is another neurochemical released as a result of hyperthermia or TBI. Following injury, NO may act as a suppressor for protein synthesis and increased expression of inducible nitric oxide synthase (iNOS) has been reported following experimental hyperthermia [8]. Besides these molecular and cellular changes, TBI patients are usually at risk for intracranial hypertension, which renders them more vulnerable to changes in body temperature because cerebral blood flow increases as temperature increases [9]. Although there may be uncoupling of this response in the injured brain, the rise in blood volume may increase intracranial pressure and leave the brain liable to further injury. Last but not least, metabolic expenditure is often increased in severely brain-injured patients. When high catabolism combines with hyperthermia, exhaustion of nutritional storage can harm tissue repair and delay recovery in TBI patients.

Hyperthermia-induced pathology in cerebral ischemia shares most but not all the mechanisms reported in TBI. After ischemic stroke, the temperature in the areas of the brain affected by ischemia is higher than the temperature in the unaffected parts of the brain and the rest of the body [10]. Increase of proinflammatory cytokines after stroke could increase brain temperature. High levels of IL-6 as well as downstream acute-phase proteins such as C-reactive protein and fibrinogen have been associated with increased brain temperature. An increase in brain temperature together with inflammatory factors can damage endothelial cells of the brain and spinal cord, causing diffusion of serum proteins through the blood-brain barrier and occurrence of cerebral edema. Focal ischemia is also known to trigger repetitive episodes of ischemic depolarization within the cortical penumbra. Ionic dys-homeostasis can lead to inordinate energy expenditure to restore ion gradients in ischemic parenchyma, resulting in the ultimate irreversible deterioration of the penumbra and expansion of the infarct zone.

Hyperthermia in Perinatal Brain Injuries

An increase in body temperature is not only deleterious in the setting of TBI or hypoxia-ischemia, but also with many perinatal brain injuries. An infant with a rectal or axillary temperature $>37.5^{\circ}\text{C}$ is considered to be hyperthermic, originating either endogenously or exogenously. Hyperthermia may reflect or produce a relative hypermetabolic state that can be deleterious to the neonate, especially to the brain. Hyperthermia can be secondary to fever generated maternally or by the neonate itself. Maternal fever, a clinical manifestation of chorioamnionitis, has been related to or at least considered as a risk factor to cerebral palsy. Infants born to mothers diagnosed with clinical chorioamnionitis, demonstrating elevated levels of IL-6 in response to infection and trauma and RANTES (products of normal T cell activation), also have elevated levels of IL-6, IL-8 and RANTES at 6 hours of age with a progressive decline. Intrapartum fever may also predispose an infant towards neurological morbidities such as neonatal encephalopathy or seizures. Hyperthermia in the context of hypoxia-ischemia or ischemic stroke has also been linked to adverse neurodevelopmental outcomes.

The message is clear that hyperthermia, especially in the brain, may aggravate the outcome of traumatic and ischemic brain injury. Even if delayed, hyperthermia worsens brain injuries. Therefore, hypothermic therapy or temperature management should be considered in time for better prognosis and outcome of patients with brain injuries.

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Hyperthermia in Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a rare but often fatal complication resulting from the use of certain medications. These include dopamine antagonists, epitomized by the typical antipsychotic drug haloperidol, as well as other drugs such as lithium, antidepressants, the antiemetic metoclopramide, and the withdrawal of drugs used in the treatment of Parkinson's disease [1].

The condition is characterized by the rapid development of elevated temperature, hyperpyrexia (a body temperature of more than 41.5°C), extrapyramidal symptoms such as tremors, dystonia (an abnormal sustained muscle contraction), and alterations in the level of consciousness. Fever associated with sweating is an almost universal sign of NMS, seen in over 98% of cases [2].

Hyperthermia is very closely linked to NMS, and fever is sometimes the only presenting symptom of the condition [3]. This close relationship has led researchers to suspect that NMS is a variant of a malignant hyperthermia, which is a genetically determined disorder that presents with an elevated body temperature upon exposure to certain anaesthetics. Mutations of proteins related to calcium homeostasis on the sarcoplasmic reticulum of skeletal muscle cells are known to cause malignant hyperthermia. In contrast, the underlying pathophysiology of NMS is still

unclear, although disturbed calcium homeostasis has been reported in NMS patients. Interestingly, NMS and malignant hyperthermia share almost identical symptoms and signs, a fact that has led to an on-going quest to determine whether NMS is similarly genetically predetermined. It is possible that NMS represents a neurogenic form of malignant hyperthermia - instead of affecting the skeletal muscles, it affects neurons of the autonomic nervous system [4].

Understanding the underlying mechanisms by which NMS develops is essential, as management of the condition is currently challenging. Withdrawing neuroleptic medications is the most important step, but NMS also improves with the administration of dantrolene, the treatment of choice for malignant hyperthermia. There is, however, no specific effective treatment for NMS and even with supportive measures the condition is lethal in approximately one in ten cases [5]. **(ak)**

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Hyperthermia Impairs Memory Functions

On extremely hot summer days, can we really perform our everyday tasks with full efficiency? Can we focus our attention on what we want? Or should we, perhaps, take at least two months off because working during summer does not make any sense?

Once again, scientists do not disappoint us by providing research on the influence of hyperthermia on cognitive processes. In a number of studies, healthy participants were exposed to high temperatures and then tested on their cognitive abilities in comparison to control groups. The results are consistent and point to the fact that hyperthermia does indeed impair short-term memory. More specifically, it influences reaction time during visual short-term memory performance, yet does not affect the accuracy [1]. Importantly, it enhances activity in bilateral dorsolateral prefrontal cortex and right intraparietal sulcus, regions important for task performance [1]. It is speculated that these activity changes are due to the higher occupation of cognitive resources in response to hyperthermia.

In other studies, it has been shown that heat exposure impairs complicated cognitive abilities, like the aforementioned visual short-term memory. However, it does not affect performance in simple tests, like attention tests [2,3]. Moreover, the authors showed beneficial effects of head cooling during hyperthermia, which preserved memory capacity, but appeared ineffective on visual recognition tests [3].

Armed with this knowledge, you always have a good excuse when something goes wrong on a very hot day. Jumping into a lake is nothing more than improving your cognitive skills! Just remember to keep a cool head, at all times! **(fm)**

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MSc Thesis Awards

Katharina-Heinroth-Preis

Outstanding research in natural sciences with a focus on biological topics from students of the three Berlin universities (Bachelor, Master, Diploma theses) are awarded with the Katharina-Heinroth-Preis of the Gesellschaft Naturforschender Freunde zu Berlin. The completion date should not be older than 24 months. Become one of the three awardees and win EUR 300. At the award ceremony, you will also present your research to the audience. Deadline for application: November 15, 2013. Further information: http://www.gnfb.de/K_H_Ausschreibung.pdf

Fever: Good or Bad?

By Silvina Romero Suárez, MSc Student Medical Neurosciences

In the 80s, a paper published by the pediatrician Barton Schmitt listed the misconceptions that parents had about their children's fever. Twenty years later, the study was repeated with shocking results: 91% of parents thought fevers were harmful, 21% listed brain damage and 14% listed death, as complications of a fever. It also revealed an excessive use of antipyretics starting at 37.8°C. Interestingly, parents reported doctors and nurses as their primary source of information about fever [1], indicating that excessive worrying about fever still prevailed among health care providers.

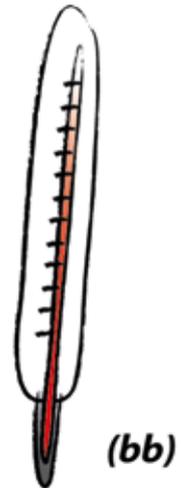
The Use of Fever

As the magnitude of a fever is associated with the severity of infection, very high fevers indicate an exaggerated inflammatory response that correlates with a decreased survival rate. On the other hand, moderate fevers are associated with a better prognosis after infection. In a study where rabbits were infected with bacteria, the survival rate increased as body temperature was elevated up to a range of 2.25°C, but when fevers above that range were present, a decrease in survival rate was observed [2].

In addition, the growth rate of pathogens is also affected at high temperatures. When ferrets were infected with the influenza virus, fewer viruses were present in their nasal cavity after fever; conversely, rabbits infected with *S. pneumoniae* kept at afebrile temperatures, had higher bacterial counts than rabbits kept at febrile temperatures. The incubation of *N. meningitidis* at 40°C resulted in a decreased growth rate

compared to the samples incubated at 37°C [2]. High temperatures also stimulate the function of lymphocytes. Elevated body temperatures in mice was shown to increase LPS (Lipopolysaccharide)-induced release of the cytokine TNF- α , mediated by NF κ B activation. In addition, the heat-shock protein 70 is upregulated after mild heat. This protein contributes to the stimulating effects of heat over macrophage cytokine production and also has antiapoptotic functions in the cells [3].

Overall, a fever is part of the 'sickness behavior' that includes lethargy, anorexia, and a loss of interest in social activities. This 'sickness behavior' is merely the response of the CNS to the alerts of an infection from the immune system in the periphery. This behavior is therefore a motivational state caused by the host to prioritize energy for activities that facilitate recovery such as rest and heat production [4].



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Hyperthermia, Heat Shock Proteins and Immunity

For years, hyperthermia has been an established therapeutic method to treat various infectious and non-infectious diseases, such as cancer [1]. Treating cancer through hypothermia involves externally heating cancer tissue to a minimum of 40 to 41°C for a certain period of time [2]. The principle on which this treatment is based remains the same for each disease.

As a matter of fact, it has been well established that an increase in core body temperature (or hyperthermia), as seen for example, when we experience a fever during a cold, strongly influences our immune response and supports our body in the fight against pathogens or our own mutated cells. One mechanism by which increased temperature modulates our immune system employs specific proteins, the so-called heat shock proteins (HSPs). HSPs are a group of proteins that help protect cells from major cell damage. Usually their expression is constitutively active, but is drastically increased when cells are exposed to elevated temperatures or other stressful events, like hypoxia, ischemia, reactive oxygen species, and many more [3]. In recent years many studies have implicated HSPs in the body's immune response against pathogens.

It has been observed that intracellular HSPs work in concert with many other proteins associated with the

antigen-presenting machinery. Thus, an infected cell is quickly degraded by proteasomes and its antigen is then translocated into the endoplasmic reticulum. MHC class I (Major Histocompatibility Complex) molecules then present this antigen on the cell surface in order to mark the infected cell for degradation by cytotoxic T-cells (CTL). Here, HSPs are bound to all the important players (proteasomes, antigenic peptides and MHC I complexes) throughout the pathway and act as molecular chaperones [4]. Furthermore, HSPs are also referred to as 'endogenous danger signals' in the innate immune response [4]. As such, HSPs are released from damaged cells and act as extracellular warning signals, which stimulate toll-like receptors and thereby activate dendritic cells. In turn, dendritic cells release inflammatory cytokines and kick-start CTL activity, thus explaining how heat helps protect the body. (le)

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Hypothermia in Wernicke-Korsakoff Syndrome

Wernicke's encephalopathy and Korsakoff's psychosis are two distinct conditions which commonly occur together and are thus grouped under the Wernicke-Korsakoff syndrome (WKS). The syndrome results from the lack of a water soluble vitamin (thiamine) and is often seen in chronic alcoholics, patients with cancer, and after abdominal surgery.

While WKS is not a direct result of chronic alcohol abuse, hypothermia is commonly encountered in people who are alcohol dependent, usually after a bout of excessive drinking. Alcohol causes widening of the blood vessels of the skin, allowing more heat to dissipate into the surroundings and lowering body temperature. Besides hypothermia, WKS is characterized by an abnormal gait, restricted eye movement, and memory loss.

Hypothermia in WKS has been suggested to be due to an involvement of the posterior hypothalamus by the underlying disease process, namely the accumulation of toxic metabolites such as lactic acid within the brain [1]. The posterior hypothalamus, also known as the mamillary region, is the main target of WKS and consists of the mamillary bodies and the posterior nucleus. Under normal conditions, the posterior nucleus is involved in the control of body temperature (thermoregulation) by causing: shivering, decreased sweating, and reduced blood supply to the skin, all of which are responses to a drop in body temperature [2].

Thiamine is essential for cellular metabolism and the synthesis of neurotransmitters, and body stores of the vitamin can be depleted within a few weeks without adequate dietary intake [3]. Thiamine deficiency damages hypothalamic neurons, although the mechanisms behind this are poorly understood. Alcohol itself has a direct neurotoxic effect

that may exacerbate neuronal loss in the hypothalamus and promote the development of hypothermia [4].

Hypothermia as a sign of WKS is important clinically, as it may be the only noticeable indication of the condition. Moreover, hypothermia has been found to persist even upon treatment of WKS with thiamine replacement, while other features of the conditions usually improve swiftly. It has also been associated with intercurrent infections which greatly worsen the prognosis of WKS [5]. **(ak)**

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Courtesy of Derek Ring

When Your Eyes Say it ... Ophthalmic Injuries

Most of us take our eyesight for granted. How many of us have even thought about the effect of the ambient temperature on our eyes?

Ocular Aging and Ambient Temperature

Accommodation, which is the ability of the human eye to focus for different distances, decreases with age. What is interesting is that the age of onset of this presbyopia seems to vary inversely with environmental temperature even after taking confounding factors such as ethnicity and altitude into account. For example, the average age of onset is between 36-40 years for temperate regions like the Philippines, the late twenties for Somalia, and between 48-50 years for those living in the Andes [1]. Given that we are homothermic species, how can we explain this relationship between presbyopia and environmental temperature? Our temperature is normally constant within our core and regions like the thighs and chest are strongly influenced by external temperature changes up to depths of at least 8mm. As the crystalline lens is located wholly or largely within this distance from the surface of the body, scientists believe that the temperature of the lens is variable and subject to external influences [2]. Furthermore, due to a lack of an external barrier like the skin, the eyes are the most sensitive parts of the body when exposed to thermal heat flux.

The Other Side of the Coin... Icy Eyes

On the other hand, under extremely cold weather conditions, corneal freezing can occur in individuals who keep their eyes open in high-wind-chill situations without protective goggles like snowmobilers and cross-country skiers. The first sign of this injury is blurring of vision, followed by pain during re-warming. The injuries are similar to those of thermal burns and treatments aim to control inflammation and secondary bacterial infections using steroids. The good news is that most injuries heal within a few days or weeks. Another common injury at high altitudes is snow blindness. This is caused by the reflection of the ultraviolet solar radiation and results in painful eyes with excessive tearing. Recovery usually occurs within 24 hours and disappears when a person rests and remains indoors.

To sum up, it is always good to keep your weather eye open! **(arm)**

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Hypothermia: The Coolest Treatment for Stroke

By Ana Klahr and Shannon Wowk, PhD Students in Neuroscience, University of Alberta, Edmonton, Alberta, Canada

Stroke kills about 20% of its victims, and survivors typically live with life-long disabilities. In the past four decades, there has been a 40-100% increase in stroke incidence worldwide, and this is expected to keep rising due to our prolonged lifespan [1]. Therefore, new stroke therapies are urgently needed. Hypothermia, or decreasing body temperature, has received considerable attention during the past two decades due to its success in ameliorating injury in other types of brain injury (e.g., cardiac arrest, hypoxic ischemic injury in infants [2]). Here we briefly review animal and clinical research on hypothermia after stroke.

Hypothermia after Focal Ischemia

Studies in the 1950s suggested hypothermia's potential to decrease brain damage during brain ischemia, in which blood flow is reduced. One of the early uses for hypothermia was as an aid to cardiac repair surgery in neonates, in which cooling protected the brain during the period when the heart was stopped [3]. The desire to use hypothermia waned as more complications became evident, such as during re-warming, and as interest grew in other therapies that were easier to administer (e.g., barbiturates) [3]. Luckily, in the 1990s, extensive animal work on hypothermia applied after global ischemia, a model of cardiac arrest, aided in the development of a more adequate cooling protocol to protect the brain. Cooling soon after ischemia for prolonged durations (e.g., several days at 32-34°C) have now consistently shown to decrease cell death and improve behavioral outcome in animal models [2,3], results that have been successfully translated to the clinic [2]. The same parameters, short delays and long durations, are also effective at reducing infarct size and improving motor function after stroke in animal models of focal ischemia [2,3].

From hundreds of putative stroke treatments [4], hypothermia is one of the most promising based upon numerous animal studies that show remarkable efficacy in a broad range of settings (e.g., different animal models) [2,3]. Unlike drugs that may target a limited aspect of the pathophysiology of stroke, cooling acts on many mechanisms of injury. For instance, cooling decreases excitotoxicity

and edema, down-regulates cell death pathways, and slows the metabolism and energy depletion, among others [2,3]. In the clinic, elevated temperature at the time of admission has been associated with worsened outcome after stroke. In fact, low body temperature is a predictor of good outlook in stroke patients [2]. So far, small clinical trials have shown that hypothermia is safe for patients with focal ischemia, even when combined with tissue plasminogen activator, a drug to dissolve blood clots, which is the current standard treatment [5]. However, its therapeutic efficacy will be determined after large, controlled, and randomized clinical trials, such as Ictus 2/3 [6] and Euro-HYP-1 [7], are conducted.

Hypothermia after Brain Hemorrhage

Intracerebral hemorrhage, or ICH, occurs when a blood vessel is ruptured creating a bleed in the brain. Unlike focal ischemia, some animal work suggests that ICH is not as influenced by temperature. While hyperthermia does not worsen injury or impair behavior after ICH, animal studies do not find that cooling consistently protects brain tissue or improves behavioral impairments after ICH. This is surprising as hypothermia improves several mechanisms of injury common to both ischemia and ICH such as reducing inflammation, edema, and blood-brain barrier disruption [2]. Cooling also provides some behavioral benefit in animal studies [2]. Thus, it is unclear why hypothermia does not consistently protect the brain after ICH. Of note, animal studies have highlighted the importance of delayed hypothermic treatment, as hypothermia initiated 1 hour from ICH onset can cause increased bleeding [2]. This is likely due to the systemic effect of hypothermia increasing blood pressure and impairing blood clotting.

While the animal literature is controversial, the clinical data on ICH and hypothermia is more promising. There have been reports from mid-19th century of cold towels placed on the heads of patients with ICH [8]. Some studies found that patients with a large ICH treated with hypothermia had lower edema and mortality rates [9] as well as better behavioral outcome up to a year after stroke [10]. Currently, there are

no controlled and randomized clinical studies completed. However, the Cooling in Intracerebral Hemorrhage (CINCH) trial [11] is currently underway.

Subarachnoid hemorrhage (SAH) occurs when a blood vessel ruptures in the subarachnoid space. Animal research suggests that hypothermia ameliorates some mechanisms of injury common to focal ischemia and ICH, such as edema. Unfortunately, animal models of SAH display limited behavioral impairments, making it challenging to assess efficacy [2]. Clinical studies suggest that fever should be prevented in patients with SAH, as elevated temperature worsens outcome and increases mortality [2]. Short cooling during aneurysm repair in SAH patients does not improve long-term outcome [2]. Large clinical trials have yet to be performed using longer periods of hypothermia.

Future Directions

Based on animal research, hypothermia seems promising for stroke patients, although large, randomized, and controlled clinical studies will test this. Still, there are many aspects of hypothermia that are poorly understood, such as how cooling parameters should be customized for different types of stroke (e.g., bleed vs. ischemia, different locations, severity), patients with comorbidities (e.g., hypertension), and when combining cooling with other therapies. Considering its potential to treat stroke, hypothermia is a challenging but exciting field of study. Further animal research will enhance the safety and effectiveness of hypothermia in order to improve the lives of those affected by stroke.

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Keeping a Cool Head: Hypothermia for Neuroprotection after Cardiac Arrest

By Rick Cornell Hellmann, PhD Student Medical Neurosciences, AG Spinal Cord Injury

Induced hypothermia (lowering the body temperature to $\leq 35^{\circ}\text{C}$) attenuates neuronal damage and provides neuroprotection mainly through lowering the rate of metabolism. It thus finds applications in ameliorating the secondary damage associated with traumatic brain injury, cardiac arrest, and stroke. This article will focus on therapeutic hypothermia after cardiac arrest.

Advantages of Hypothermia

For each degree centigrade decrease in body temperature, cellular metabolism is reduced by 5-7%, but the observed neuroprotective effect of hypothermia is much greater than can be explained by reduced metabolism alone [1].

During hypothermia the brain is exposed to fewer excitatory neurotransmitters and has more time to clear free radicals. It also reduces the average kinetic energy and hence the velocities at which free radicals travel, effectively lowering the likelihood that a free radical can damage vital cell parts before it gets neutralized by the endogenous anti-oxidative system.

Altogether, hypothermia induces a favorable shift in intracellular concentrations of ions and metabolites such as inorganic phosphate, lactic acid, Ca^{2+} and H^{+} , hence slowing brain acidosis [1].

Hypothermia Studies

Animal studies of therapeutic hypothermia have shown profound neuroprotective effects [1]. Despite being the most used model, the small rodent brain is structurally, dimensionally, and metabolically different from the proportionally bigger and complex human brain. Therefore, it probably shows a greater response to neuroprotective efforts. Unlike with rodent models, human studies must take into consideration different temperatures, duration of therapy, therapy onset/ending, cooling methods, and factors such as age, gender, and

pre-existing illness [1,2]. Clinical studies of hypothermia after cardiac arrest have therefore produced strongly inconsistent results.

The two largest recent controlled studies on humans have shown significant improvements in patients' neurological outcome and survival. The European study on "Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest" showed a reduction in mortality by 14% and a 16% increase in patients with a good neurological outcome (able to live inde-

pendently 1/2 year after cardiac arrest) in the hypothermia group. The 2002 Australian study on "Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia" demonstrated a 26% increase in patients with a good neurological outcome [1,3].

Many adequate cooling methods are available and, with advancing medical technology, even more have become available recently. One such new device is an intravascular heat exchanger [3], which allows for rapid cooling and exact monitoring of blood flow and temperature. Another new internal cooling method is the intravenous infusion of iced isotonic fluid, such as saline solution [2,3]. Because saline solution is readily available even in a pre-hospital setting and safe to use regardless of age or gender, this is a suitable candidate for the early

initiation of hypothermia. It is nevertheless necessary to maintain the cooled state with other methods later [2,3].

External methods include the application of ice packs to areas with a high heat exchange capability like the armpits, neck, groin or the head in the form of a cooling helmet [3,4]. However, proper placing of these devices requires a breach of privacy, especially when carried out in a pre-hospital setting. In addition the rate of cooling is relatively slow. Alternative methods include the use of cooling blankets or wet-evaporative cooling [4].

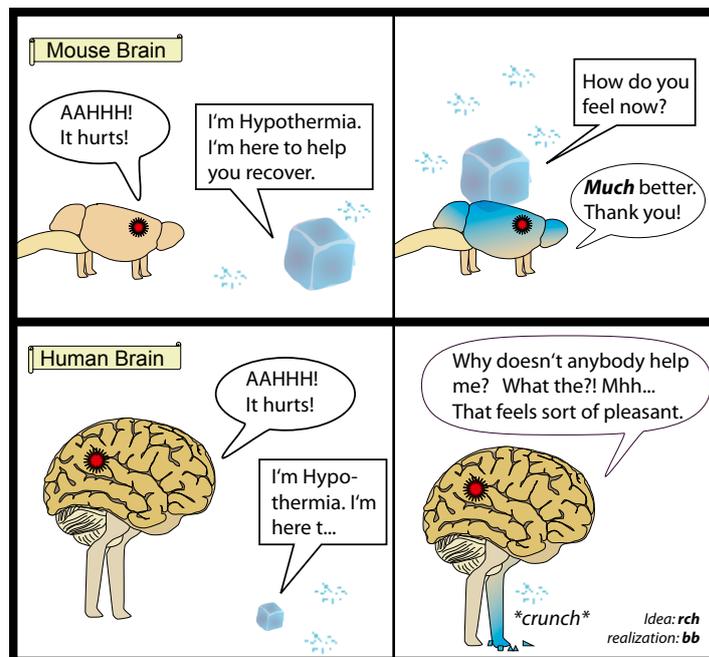
Hypothermia should be initiated as soon as safely possible but homeostatic imbalances induced by ischemia and the physical insult of reperfusion will persist for days.

Hence there is a long time window (48-72h) to initiate and maintain hypothermia.

Any one cooling method alone has shown lower efficacy than two or more methods combined. That and the rapid invention and inclusion of new cooling methods is one reason why an optimal therapy has not been developed and should therefore be researched and compared across qualified hospitals around the world.

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- [2] Peberdy et al, Circulation, 2010
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pendently 1/2 year after cardiac arrest) in the hypothermia group. The 2002 Australian study on "Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia" demonstrated a 26% increase in patients with a good neurological outcome [1,3].

Cooling Methods

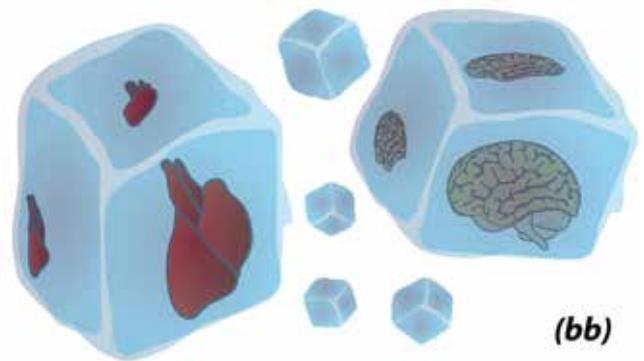
Cooling must be accompanied by the use of sedatives and neuromuscular blockers, otherwise treatment will cause shivering and hence re-warming of the body with a counterproductive increase in energy/oxygen consumption. A good treatment protocol and adequate monitoring is required to successfully apply hypothermia.

Cognitive Outcomes after Hypothermia Therapy in Cardiac Arrest Patients

By Charlotte Klein, PhD Student Medical Neurosciences, AG Neural Regeneration and Plasticity

Hypothermia therapy is commonly used in patients with out-of-hospital cardiac arrest improving the survival rate after resuscitation from about 1 in 6 to approximately 1 in 2. Wonderful news - but even though so many patients survive, what if most of the survivors are severely cognitively impaired and suffer from poor quality of life? Alejandro Rabinstein, MD, from Mayo Clinic, Rochester, Minnesota, addressed this major concern by initiating a study to measure cognitive outcomes with therapeutic hypothermia after cardiac arrest. Initial data, presented at the American Academy of Neurology (AAN) 65th Annual Meeting in March 2013 (Abstract S07.004), suggest that most of the patients who do survive after hypothermia have preserved cognitive function and are able to return to work. Of the patients who took part in the Telephone Interview for Cognitive Status (TICS-m), which is described as a short simple cognitive tool, 60% were considered cognitively normal and 40% were mildly cognitively impaired. Almost 80% of the patients who were working up to the time of cardiac arrest returned to work. It was stated that cognitive outcome was not associated with age or time to the return of spontaneous circulation.

Therapeutic hypothermia is thought to help in reducing the risk of ischemic injury to tissue following a period of insufficient blood flow, as is the case after cardiac arrest. Neuronal cells are particularly sensitive to hypoxia, a consequence of insufficient blood flow. A comparative study



assessing cognitive functions in patients after cardiac arrest who underwent therapeutic hypothermia or not - to my knowledge - has not been accomplished so far, but might be of interest to evaluate the potential neuroprotective effect of hypothermia therapy and hence give an insight into its clinical efficacy beyond the mere survival rate of patients.

Reference

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E-Learning Course "Cardiac Arrest, Hypothermia and Resuscitation Science"

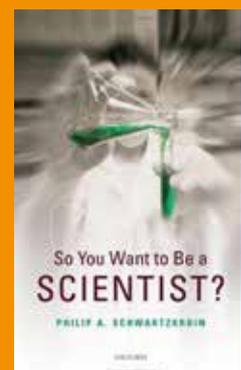
Did our current issue inspire you to learn more about hypothermia and its application as a potential treatment for cardiac arrest and brain diseases? Then check out the e-learning course "Cardiac Arrest, Hypothermia, and Resuscitation Science" from the University of Pennsylvania

on Coursera. It explores the breakthroughs in treating patients with cardiac arrest, and is not solely about hypothermia. The course took place in May 2013 but can be reviewed. You can also enroll in future sessions. For more information: <https://www.coursera.org/course/cardiacarrest> (mz)

Contest

We are always interested in including your contributions. You can submit anything you see fit on the topic of neuroscience. Send us your most exciting microscopic pictures, or a creative photo, thoughts on neuroscience or self-written poems - whatever comes to mind! The best contribution will be published and rewarded with **the book "So You Want to Be a Scientist?"**. So, what are you waiting for? Start the engine of your mind and get going! Trust us, it is worth participating! Send your contribution to cns-newsletter@charite.de to win the Medical Neurosciences shoulder bag. **Deadline for submission for the next issue: October 31, 2013.**

This issue's winner is **Tian Zhang** who contributed two articles to this issue's: "The Role of Hyperthermia in Brain Injuries" and a conference report about "The Most Specialized Community for Blood Brain Barrier". Thank you very much for your contribution.



Cooling – Hope after Neonatal Hypoxic-Ischemic Encephalopathy

Birth is a joyful yet critical event. In most cases, delivery goes as planned and a healthy baby is born into the world. In 0.2-0.4 % of cases, however, a fetus with normal intrauterine development suffers from neonatal hypoxic-ischemic encephalopathy [1] during delivery and consequently dies or develops a lifelong neurodevelopmental disorder.

Oxygen is delivered to the fetus through the placenta and therefore placenta praevia, maternal hypotension, uterine rupture, a prolonged time spent in the birth canal due to a malpositioned fetus and weakening of uterine muscles often result in such injury [2]. Due to the characteristics of fetal brain maturation, full-term babies are at greater risk for damage than preterm babies [3]. While hypoxia can affect the whole body, its effects on the brain are the most detrimental, as damage to this region is the least controllable and often irreversible.

Under the above mentioned unfortunate circumstances, it is almost impossible to avoid hypoxic-ischemic encephalopathy in otherwise healthy newborn babies and treatment or damage control in these babies is- due to the fragile nature of the organism and of the central nervous system- challenging. Nevertheless, some hope to improve the quality of life and reduce the mortality of children suffering from neonatal hypoxic-ischemic encephalopathy exists through hypothermic whole body cooling, which is implemented until an esophageal temperature of 33.5°C is reached [4]. When initiated within the first 6 hours of life and maintained for 72 hours followed by slow warming in 0.5°C intervals, hypothermic therapy can reduce the likelihood of death or moderate to severe neurodevelopmental disorders (assessed at 18-22

months of age) by 18 %. Supposedly, this protective effect is partially due to suppression of pathways leading to delayed cell death [5].

Hypoxic-ischemic encephalopathy in normally developed fetuses at the time of birth is a tragic and relatively uncontrollable event in which medicine has previously been powerless. New light is delivered to the families and babies that have suffered from hypoxic-ischemic encephalopathy by recent advances showing reduction in disabilities and mortal outcome by extensive hypothermic therapy. **(cr)**



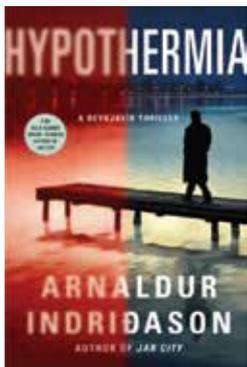
Courtesy of Kiva Atkinson

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- [5] Shankaran, J Neurotrauma, 2009

Arnaldur Indriðason – Hypothermia

By Charlotte Klein, PhD Student Medical Neurosciences, AG Neural Regeneration and Plasticity



There are three stages, Erlendur remembers, because he has read a lot about hypothermia, to understand the phenomenon. First undercooling leads to a death-like state and with decreasing brain activity to slow passing away. "The loss of one or two degrees Celsius of body temperature leads to involuntary shivering and numbness in the hands [...] During the second stage, when the body temperature can drop by as much as four degrees, the lips, ears and

fingers turn blue. During the third stage, the body temperature falls below thirtytwo degrees Celsius. Shivering ceases, speech and thought are impaired and the victim feels drowsy. The skin turns blue and mental functioning and sensations become increasingly irrational. Eventually, the organs fail and clinical death ensues. Yet brain death is not instantaneous as the cold impairs cell deterioration, slowing damage to the cerebral tissue."

Hypothermia is the 11th volume of this crime series, and

it will be the last. The story is about police inspector Erlendur only; his colleagues from the murder squad in Reykjavik no longer play a role. Erlendur travels to the eastern fjords again, where he stays in his former, now dilapidated, childhood home. As usual, he broods over the tragic loss of his - at that time - eight-year-old brother Bergur during a snowstorm. Not only does this open case of a missing person - Bergur's dead body has never been found - prey on Erlendur's mind, but also the case of a young woman, who disappeared in 1942 during a thunderstorm. Erlendur is not there as a policeman, but as a private citizen. However, he is obsessed with the idea of elucidating the fate of missing Matthildur. Despite the lapse of time of 60 years and due to his determined curiosity, Erlendur manages to shed light onto what happened on that January night.

The rhythm of narration is slow but nevertheless fascinating, and fits well to what is said about the process of hypothermia. The end leaves room for speculation and different interpretations. The sense of guilt and grieve about the loss of a beloved person is heavy. Adding the descriptions of a sparse and barren countryside on the cusp of another long, cold winter with interminable darkness, this book is not suitable for people with melancholic tendencies.

TRP Channels – Our Bodies' Thermometers

Although not always recognized, our ability to perceive drastic changes of temperature in our surroundings is crucial for survival. Extreme heat or cold can cause irreversible tissue damage or even death, often by disturbing enzyme activity, which is functional at a very narrow optimal temperature range. Thus, we need to guarantee that our core body temperature remains at 37°C at all times.

The detection of any kind of somatic information such as touch, pain or temperature is dependent on specific somato-sensory neurons. Generally, somato-sensory neurons are special in that they have one axon with two specialized branches. While one branch projects into the periphery and reaches out to outer layers of the skin, the second branch terminates in the CNS and leads to processing of the peripheral stimuli. In order to separate the different sensory modalities, it is vital that sensory neurons supposed to detect one specific signal, only get activated by that specific stimulus. As a consequence, temperature-sensing neurons carry a specific set of receptors, which are activated by particular temperature conditions. In that way, just like tiny thermometers, these receptors can make the CNS aware of the temperature changes in the outside world [1].

Accumulating evidence suggests that the main temperature sensors in mammals all belong to the transient receptor potential (TRP) superfamily of cation channels, which is further divided into six subfamilies. Within these subfamilies, only six receptors have thus far been identified as specifically temperature-sensitive and include TRPV1, 2, 3, 4, TRPM8, and TRPA1. Together, and with their unique properties, they are able to detect the entire temperature spectrum.

In more detail, TRPV1 and TRPV2 are activated by strong heat above 43°C, while TRPV3 and 4 remain in a spectrum of sensing moderately warm and 'fuzzy' temperatures [1]. In contrast, TRPM8 and TRPA1 belong to the cold-sensing receptors.

Burn, Baby, Burn

TRPV1 was one of the first receptors to be identified, in 1997 [2], and is a calcium cation channel which is activated by high temperatures (above 43°C). Interestingly, TRPV1 is not only activated by heat, but also by other molecular ligands, such as capsaicin, the compound

in chili peppers that elicits a burning sensation. Thus, it has been hypothesized that TRPV1 also conveys painful stimuli, related to heat [3]. Although the nociceptive functions of TRPV1 have not yet been fully corroborated in vivo [4], it has been established that tissue acidification (which can occur during pathological conditions like ischemia) and inflammatory molecules, like bradykinin, nerve growth factor or prostaglandins, can shift the temperature sensitivity of TRPV1 to a lower range [5]. This could explain why inflamed tissue is much more sensitive to heat than normal tissue (also referred to as heat hyperalgesia).

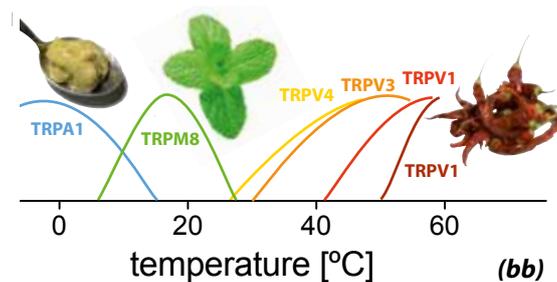
In contrast, TRPV2, another receptor which detects temperatures over 52°C, is insensitive to capsaicin as well as low pH [1]. However, extensive evidence suggests that TRPV2 conveys the painful sensation that accompanies such elevated temperatures and is responsible for noxious heat sensation. Therefore it has been proposed that this receptor is expressed in sensory neurons which carry lightly myelinated A- fibers. These fibers transmit nociceptive information much faster than unmyelinated C fibers, which seem to exclusively be associated with TRPV1 [3].

Warm and Fuzzy Feeling

TRPV3 and TRPV4 fire at temperatures fluctuating around body temperature. Here, TRPV3 has been found to activate when temperature ranges from 34 to 38°C, while TRPV4 is active at temperatures between 27 and 35°C [3]. One interesting feature is that both are not predominantly expressed in sensory neurons, but in skin cells, the keratinocytes [5]. However, both receptors differ in that TRPV3 is sensitized by repeated heating, while the activity of TRPV4 is not influenced. Hence, the responses elicited in TRPV3 receptors increase stepwise, when they are repeatedly heated up. This makes TRPV3 active at both harmless warm and dangerous noxious temperatures. In effect, this mechanism could warn an organism of a potentially damaging stimulus [1].

Getting Through a Hard Winter

Finally, TRPM8 and TRPA1, two different cold-sensing receptors, may help survive an organism when temperatures become dangerously low. As such,



TRPM8 is strongly activated by cooling below 28°C. Additionally, it has been found that TRPM8 can be activated by menthol, the chemical agent found in mint which could provide an explanation as to why fresh mint tastes so refreshing. Furthermore, it has been shown that TRPM8 knockout mice fail to discriminate warm from cool temperatures and show no preference for temperatures that would allow them to sustain a more efficient body temperature level [5].

Similarly to TRPV2, TRPA1 is not sensitive to chemical ligands, and can thus not be activated by menthol. Also, this receptor is activated by temperatures much lower than TRPM8 (below 17°C) and belongs to sensory neurons that convey pain sensation. In fact, TRPA1 is specifically common in sensory neurons that express nociceptive markers. This has led to the suggestion that TRPA1 is involved in cold nociception [3]. Strikingly, TRPA1 has also been found to co-express with TRPV1. This shows that some sensory neurons may convey stimuli of both noxious heat and cold [1]. In effect, this might explain why we sometimes paradoxically associate ice-cold temperatures with a painful burning sensation.

All in all, and although a vast mass of information on the mechanisms of thermo-sensation still needs to be accumulated, it seems that a strikingly small number of specific thermo-receptors can work together and create a full temperature profile of our environment. We should not take them for granted; after all, it is those little thermometers that enable us to keep cool in the summer days that hopefully are here to stay. **(le)**

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- [4] Pogorzala et al, J Neurosci, 2013.
- [5] Talavera et al, Trends in Neurosci, 2008

Hypo-/Hyperthermia-Based Clinical Trials

Name of the Study	Aggressive Fever Control With Intravenous Ibuprofen After Non-traumatic Brain Hemorrhage
Disease	Fever After Non-traumatic Brain Hemorrhage
Intervention	Intravenous Ibuprofen
Aim	The purpose of this study is to assess whether ibuprofen given intravenously is more effective in combating fever than the current standard of care. Should results from this study demonstrate that ibuprofen infusion is effective, a larger study will be conducted to determine whether this aggressive fever control regimen leads to improved recovery after brain injury.
Study Design	Randomized
Status	Phase IV
Sponsors and Collaborators	Columbia University, Cumberland Pharmaceuticals

Name of the Study	Temperature Control in Central Fever in the Neuro-ICU
Disease	Fever - Brain Hemorrhage
Intervention	Device: Gaymar Rapr-Round (external cooling blanket)
Aim	There are few treatments for central fever (fever that is due to the central nervous system, as opposed to an infectious source). It is hypothesized that an externally applied cooling blanket will reduce temperature in neurologically ill patients with central fever.
Study Design	Interventional
Status	Phase IV
Sponsors and Collaborators	Northwestern University, Gaymar Industries, Inc.

Source: <http://clinicaltrials.gov> (*mlr*)

Perception Leads Reality – The Effect of Temperature on Perception

Perception, defined as the organization and identification of sensory information in order to represent and understand our environment [1], is in a state of constant flux. It should come as no surprise then, that even our body temperature can affect our perception.

Experiments have shown that our perception of time speeds up when our body temperature is increased above normal and decreased when our body temperature is cooled below normal [2]. The most common hypothesis for this phenomenon is that we have a temperature-sensitive biological or chemical clock and that temperature manipulation produces changes in arousal. Perhaps this explains why when we have a fever our sense of time is also warped!

Hypothermia also seems to affect our visual perception. In an EEG study of face recognition, it was found that hyperthermia accelerates the early stages of visual perception. In this experiment, upright and inverted faces were presented to two groups of participants, a control and a hyperthermic group. The hyperthermic group had earlier latencies in the two EEG peaks of interest, the P1 and N170. However, the specific face sensitive response, the N170 had a significantly smaller amplitude in the hyperthermia group when compared to the controls. Furthermore, the inversion

effect of the faces on the N170 remained unaffected. This result suggests that although hyperthermia impairs the detection of faces in the visual field and their initial streaming to face-specific structural mechanisms, the subsequent face-specific configural processing remains unaffected [3].

With respect to odor and taste perception, while the exact effect of our body temperature on odour perception remains unexplored, we know that temperature or heating itself increases the odour of a substance due to the release of volatile molecules. Furthermore, odour ratings rise when the temperature increases when samples are sniffed. However, ratings made retronasally rise only for solids and not liquids. This is thought to be because liquids reach body temperature faster than solids when placed in the mouth. [4]. As the prominent English writer Aldous Huxley says, "There are things known and there are things unknown, and in between are the doors of perception." (*arm*)

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Guido Guenther

A Conversation with Guido Guenther, MSc Medical Neurosciences



Guido was a student in the Medical Neurosciences MSc program from 2004 to 2006. After graduating, he specialized in Clinical Neurology in Mexico City and is currently working there as a clinical neurologist and a Neurology professor at La Salle University.

MZ: What was your scientific background before you joined the program?

GG: I studied Medicine before I joined the program. Being a medical doctor helped me to be familiar with the normal and pathological functioning of the nervous system and the rest of the human organism. As a physician, I had the advantage of knowing the clinical field where many discoveries in basic science find their final use. The MedNeuro Program helped me complete my scientific background in terms of basic scientific research.

What motivated you to join the Medical Neurosciences Program and how did you benefit from it?

My main motivation was my affinity to neurology and neuroscience. The program brought me many professional benefits such as international lab, aca-

demical research, and clinical experience. During my time at the Charité, we had the opportunity to get in touch with researchers from the major fields of neuroscience research, such as learning and memory, neuroprotection, functional neuroimaging, biological rhythms, and many others. In my thesis at the MDC in Berlin Buch, under the supervision of Prof. Kettenmann, Prof. Kronenberg, and Prof. Endres, I investigated the pharmacological characterization of rat cultured cortical neurons using calcium imaging. Apart from science, the program has also brought me many personal rewards such as new friends.

What is your main research question and what are you working on now?

I am working as a clinical neurologist as well as a Neurology Professor at La Salle University. Recently, I started a research collaboration with an engineering company in the area of telemedicine/tele-neurology.

This sounds interesting. Can you explain what telemedicine is?

The field of telemedicine is a fast growing field in medicine that is oriented to maintain health or restore it without the need of a direct, physical interaction between patients and doctors. This can be achieved through the development of new technologies (hardware and software) or using the existing ones to carry out a medical interview, physical examination with the aid of a health technician and specialized lab and imaging studies. Instead of going to the hospital, the hospital can go to your house or rural clinic.

What is research like in Mexico? What are the main challenges and what is the beauty of it?

Research in Mexico is like research in most labs across the world, including some of the most common limitations like low budgets for scientific research

or difficulties hiring enough lab personnel. An important limitation of some countries like Mexico is the need to import most of the research goods such as reactors and so on.

What are your aspirations in your current position?

I expect to continue growing and developing as a clinician and a researcher. Through my work, I would like to contribute to the building of a network of services that make telemedicine and specifically, teleneurology possible. I consider teaching and mentoring very important. It is a way to create an interest in the younger generations and helps to keep alive ongoing research projects.

Where do you see yourself in 10 years from now?

I see myself teaching, researching, and working as a clinician at the same time - challenging, but worthwhile.

What other passions do you follow besides neuroscience?

I am interested in reading and biking. Now I am reading "In Search of Memory" by Eric Kandel. One of my favorite science books is Cosmos from Carl Sagan. Biking in Mexico City is enjoyable on Sundays when some nice streets are closed to cars and only bikers, runners, walkers, and skaters can use them.

Do you miss Berlin?

I miss my friends particularly. I also miss the many museums and their good exhibitions like the ones in the Neue Nationalgalerie. I used to go biking in the Tiergarten and spend time at the Mauerpark on weekends. There were several restaurants that I enjoyed very much on the Kantstrasse, like a Chinese one called Happy Friends.

Thank you, Guido. (mz)

Awards of the DGKN: Alois-Kornmüller-Preis and Nachwuchspreis Neurosonologie

The German Society for Clinical Neurophysiology and functional Imaging offers to awards for young scientists below the age of 35 of €3500 each: The Alois-Kornmüller-Preis for excellent research in the field of clinical neurophysiology and the Nachwuchspreis Neurosonologie for research in neurosonology. Deadline: September 30, 2013. More information: <http://bit.ly/10x8IOY>

Mexican Restaurants in Berlin

By Silvina Romero Suárez, MSc Student Medical Neurosciences

The only cliché that is true about Mexican food is that we like it hot. The average Mexican consumes 15kg of chili per year [1]. The capsaicin in chilli causes a burning sensation by activating TRPV1 channels. There are more than 40 varieties of chillies in Mexico, each of which has a different flavor and hotness, with the habanero being one of the hottest in the world. Read on to learn about some restaurants in Berlin that will give you a hot kick and quite an accurate notion of Mexican food.

Ta' Cabrón (Skalitzer Strasse 60, 10997 Berlin)

Try the tacos! Although the homemade tortillas are rather soft, the fillings are authentic and flavourful. Cochinita pibil, which is shredded pork cooked with achiote, guajillo chili, and orange juice is one of the best, available also in the vegetarian version with soya. The shrimp tacos are always delicious and for the blutwurst lovers there are moronga tacos. Tostadas the tinga, which is chicken cooked in a mild tomato chipotle sauce over crunchy tortillas, are also good. Do not forget to taste the seasonal dishes like pozole and tamales that are hard to find in other places. Mexican beers besides Conona, like Bohemia, and Tecate can be found here.

Chaparro (Wiener Strasse 14, 10999 Berlin)

We have been coming back to this place for two reasons: they have carnitas and barbacoa. Carnitas is a popular dish that consists of pork that is first deep fried in its own fat and then

slowly cooked in a huge copper vessel. This results in very soft meat with crispy edges; barbacoa, another speciality, is slow cooked steamed beef that gives rise to very tender and flavorful meat. A dash of green, red or habanero salsa along with a few drops of lime and you have the perfect taco.

The More Hyp and Less Authentic Marias

Maria Peligro (Skalitzer Strasse 81), Maria Bonita (Dazinger Strasse 33) and Santa Maria (Oranienstrasse 170) have some traditional food like camote (sweet potato), tacos campechanos and enchiladas. And finally, the restaurant Papalotl in Belforterstrasse 22, experiments with modern Mexican cuisine. Although a bit overpriced, I really recommend their big selections of artisanal Mezcal, that can be enjoyed alone or in an original cocktail



Tamarindo-Mezcal cocktail at Papalotl

Reference

[1] geo-mexico.com

Motor Neuron Disease Documentary Screening at the Charité

In June, the Charité's International Graduate Program Medical Neurosciences hosted an exclusive screening of the motor neuron disease (MND) documentary "I Am Breathing" in Berlin. Produced by a team from Edinburgh, the screening was attended by an audience of young neuroscientists and members of the general public.

Despite being rare, MND, possesses many unique features that highlight its importance. It is a combination of several distinct conditions and is characterized by a specific loss of the nerves that control movement. The disease affects those in the prime of their lives, is relentlessly progressive, and typically fatal within a few years. Cognition is left completely intact (as is sensation), and thus patients afflicted with MND are usually lucid and aware of the devastating deterioration occurring within their bodies throughout the course of the illness.

Scientifically, MND is quite the curious malady. It affects motor nerves in the central and peripheral nervous systems

indiscriminately, yet spares all other nerve types. It does not improve with currently available treatment strategies which other similar neurological disorders respond to, such as immunosuppressants and immune modulating drugs. This is probably because there is very little inflammation in MND - the nerves simply degenerate and die, with little response from the body.

The film itself was very touching. It follows Neil - a man dying of MND as he attempts to deliver a final message to his infant son. Neil's sense of humor was remarkably intact throughout his battle with MND, and despite the grave theme of the film, he consistently made the audience laugh. Although the audience had a difficult time understanding the thick Scottish accents, everyone in attendance definitely learned something valuable from the film. (ak)

More info

www.iambreathingfilm.com

Young Scientist Award 2013 of the Competence Network Stroke

Excellent clinical or preclinical research in the field of stroke by a young scientist (not older than 36 years) can be awarded with 2000€. Deadline: October 31, 2013. More information: <http://bit.ly/12mhZEB>

Berlin Brain Days

2013 / NOV. 20–22

0 Opening lecture

Fernando Nottebohm
The Rockefeller
University

1 Keynote lecture

Robert Edwards
University
of California
San Francisco

2 Keynote lecture

Simon Thorpe
Centre de Recherche
Cerveau &
Cognition, Toulouse

3 Keynote lecture

Silvio Rizzoli
European Neuro-
science Institute
Göttingen

4 Keynote lecture

Amanda Sierra
University
of the Basque
Country

5 Keynote lecture

Rajiv R. Ratan
Burke Medical
Research Institute,
New York

6 Ph.D. talks

15 talks
by Berlin Ph.D.
candidates & guests

7 Posters

Poster presentations
by Berlin Ph.D.
candidates & guests

Opening ceremony

Nov. 20, 18.00, Humboldt-Universität zu Berlin,
Campus Nord, Haus 2, Hörsaal 1 (entrance
to campus from Luisenstraße 56, 10117 Berlin)

Nov. 21–22, 2013

Max Delbrück Center
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www.neuroscience-berlin.de/bbd/

The Most Specialized Community for Blood-Brain Barrier

10th International Conference on Cerebral Vascular Biology, Montreal 2013

By Tian Zhang, PhD student Medical Neurosciences, AG Clinical Neuroscience

With roughly over 250 participants representing more than 20 countries, the 10th international conference on cerebral vascular biology may not have been the largest, but is definitely the one for those with a passion for the natural mystery of the Blood-Brain Barrier (BBB) and the Neurovascular Unit (NVU) in both healthy and diseased conditions. By joining the program packed with keynote and oral presentations, poster sessions and other social events, I got the chance to rub shoulders with leading researchers in cerebral vascular biology and opportunities of learning and networking.

The talks were categorized into nine main domains, which broadly covered the most interesting topics in cerebral barrier development, molecular composition and cell-cell interactions in the neurovascular unit (NVU), NVU inflammation and immune cell migration, neurovascular coupling in diseases and new drug delivery. The inspiring and thought provoking talks, kept the discussions lively and the magically beautiful images of cerebral vasculature left me awestruck.

Targeting Metabolism in Angiogenesis

Peter Carmeliet, Professor of the Catholic University of Leuven, compared the metabolic similarity between tumor growth and that of angiogenesis, both of which switch from aerobic respiration to glycolysis for energy generation. Based on this, they explored the anti-tumor potential by pharmaceutically blocking glycolysis *in vivo*. It turns out that a 50% systemic reduction of glycolysis has the best

curative effect and is tolerable. Anti-glycolysis therapy seems promising compared to anti-angiogenic therapy targeting vascular endothelial growth factor (VEGF) receptors, since anti-VEGF treatment has at best, only transitory therapeutic efficacy followed by resistance.

Dynamics of T Cell Activation in Real Time During CNS Autoimmunity

Alexander Flügel, Professor of the University Medical Center, Göttingen, gave an exciting talk about the dynamics of T cell activation during central nervous system (CNS) autoimmunity. They combined the fluorescently labeled nuclear factor of activated T cells (NFAT) with histone protein H2B to intravitaly visualize T cell activation. The first test has been made in experimental autoimmune encephalitis, where they reported that effector T cells entering the CNS become activated after short contacts with leptomeningeal phagocytes and this process is extended to the parenchyma during established disease. Thus, it proves that the intensity and duration of the disease depends on the activation process during the preclinical phase rather than during the established disease.

If you are fascinated by research on the BBB and NVU and want to know about state-of-the-art vascular biology, CVB 2015 should already be marked on your calendar!

References

- [1] Potente et al, Cell, 2011
- [2] Lodygin et al, Nat Med, 2013

5th G-Node Winter Course in Neural Data Analysis

By Nikolas Karalis, MSc Student Neurasmus

The fifth edition of the yearly G-Node Winter Course on Neural Data Analysis [1] took place at the end of February in Munich. It was organized by the German Neuroinformatics Node, [2] part of the International Neuroinformatics Coordination Facility. Participants from diverse neuroscientific backgrounds - both theoreticians and experimentalists - got hands-on experience with neural data analysis during this intense week.

The course consisted of four different topics, each spanning a full day of theoretical introduction and practical sessions. On the first day, Clemens Boucsein (ALU Freiburg) introduced techniques for the detection and statistical description of spontaneous as well as evoked post-synaptic currents from whole-cell patch-clamp recordings. The second day was devoted to modeling short-term synaptic depression under the supervision of Alex Loebel (LMU Munich). The spectral analysis of spiking data was addressed on the third day, during which Jan Grewe (LMU) guided us through the implementation of various statistical measures of spiking activity. The last day, in a module designed by Martin Nawrot (FU Berlin), we analyzed the directional tuning in single unit

activity from the monkey motor cortex.

The course is targeted to researchers interested in the practical analysis of data complemented with a theoretical approach. Matlab programming skills are a prerequisite, which are further crafted during this practical course of day-long coding and data analysis. All in all, this crash course on basic and more advanced neural data analysis techniques is very useful for those already working with or planning to start working with neural data and can help boost your data analysis abilities.

The next meeting of the G-Node team is called the Advanced Scientific Programming in Python, a summer school organized by the University of Zurich and G-Node from the 1st-6th September 2013, followed by the Bernstein Conference 2013, which will take place on September 25-27, 2013 in Tübingen.

References

- [1] <https://portal.g-node.org/dataanalysis-course-2013/>
- [2] <http://www.g-node.org/>

Open Positions for PhD and Master Students in Neuroscience Research in Berlin

Type: Master Thesis Project/Lab Rotation

Project Title: Mesenchymal stem cells in a hemiparkinson rat model
Field of Research: Stem cells, parkinson, regeneration, and plasticity
Possible starting date/deadline for application: As soon as possible
Research Group: AG Barbara Steiner, Neural Regeneration and Plasticity
Contact: Anne Schwerk, anne.schwerk@charite.de, tel.: 030 450 517295

Type: Lab Rotation/Master Thesis

Title: Behavioral and neurochemical effects of Deep Brain Stimulation in animal models of psychiatric disorders (applied methods: surgery, behavioral testing incl. intracranial self-stimulation, immunohistochemistry)
Field of Research: Deep Brain Stimulation as a potential treatment for therapy-resistant psychiatric disorders
Starting date: Immediately
Research group: AG Christine Winter, Experimental Psychiatry
Contact: Julia Rummel, julia.rummel@charite.de, tel.: 030 450 525016

Type: PhD Position in Experimental Neurophysiology

Title: Network oscillations in the hippocampal area dentata
Field of research: The available position is part of a project examining the emergence and maintenance of neuronal network oscillations in the hippocampal formation, particularly gamma oscillations in the dentate gyrus region. In this project, the PhD candidate will use electrophysiological, morphological, and potentially imaging techniques to unravel mechanisms underlying these network oscillations. The ideal candidate will be highly motivated and team-oriented, with a strong interest in neurobiology and an aptitude for data analysis. Prior research experience in electrophysiology techniques is advantageous, but not an absolute requirement. Candidates should hold a Master's degree or equivalent in Neuroscience, Biological Science, Biomedical Engineering, or a related field. To apply, please email a statement of motivation, current CV, and 1-2 references.
Research Group: AG Dietmar Schmitz, CCO, Neuroscience Research Center
Contact: Anja Gundlfinger, anja.gundlfinger@charite.de, tel.: 030 450 539004

Neuroscience in Your Everyday Life

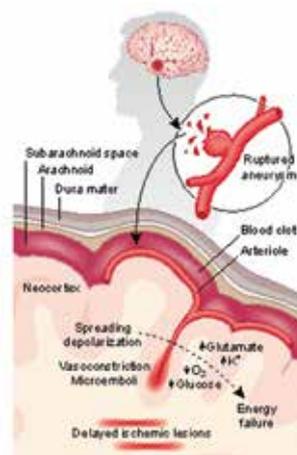


Why is it Again that Blood is Toxic to the Brain?

Imagine that the brain is the most popular club in town- everyone wants in! Of course a hip club needs someone to regulate the crowd - a bouncer. In the brain's case it is the blood brain barrier (BBB). The BBB protects the brain from toxins but also from variations in blood composition which could occur due to meals, stress or exercise.

Now what happens when the BBB is damaged on a large scale? Basically, all hell breaks loose! This is the case, for example, in a subarachnoidal hemorrhage (SAH), or in an intercerebral hemorrhage (ICH). These can be caused by the rupture of an aneurysm, a traumatic brain injury or stroke, resulting in the accumulation of extravasated blood and an elevation of intracranial pressure. Immediately, cerebral blood pressure and the delivery of oxygen and glucose to the lesion area are reduced amongst other reasons due to vasospasm [1]. This leads to the occurrence of brain edema, and ultimately neuronal cell death. There are a number of pathways that have been implicated in neuronal cell death: hypoxia, oxidative stress, inflammation and excitotoxicity [2].

15 % of all strokes are caused by an ICH [3]. Here, the lesion area expands from the foci of the stroke due to spreading cortical depressions, a self-propagating wave of neuronal



Delayed ischemic lesion (Iadecola et al, Nat Med, 2009)

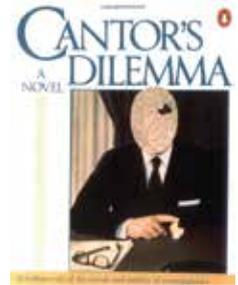
and glial depolarization [4]. Comparable to this, in SAH cases independent of stroke, delayed ischemic lesions (DILs) are formed by a similar mechanism (fig. 1). DILs are massive stroke-like lesions that develop days after the bleed and are a major cause of disability and death. SAHs have high mortality rates ranging from 40-50 % [1] and often leave surviving patients with severe impairments.

Although most of the underlying pathophysiology has been discovered, the treatment remains elusive. (vi)

References

- [1] Iadecola et al, Nat Med, 2009
- [2] Cahill et al, Stroke, 2007
- [3] Wang et al, J Cereb Blood Flow Metab, 2007
- [4] Dreier et al, Brain, 2009

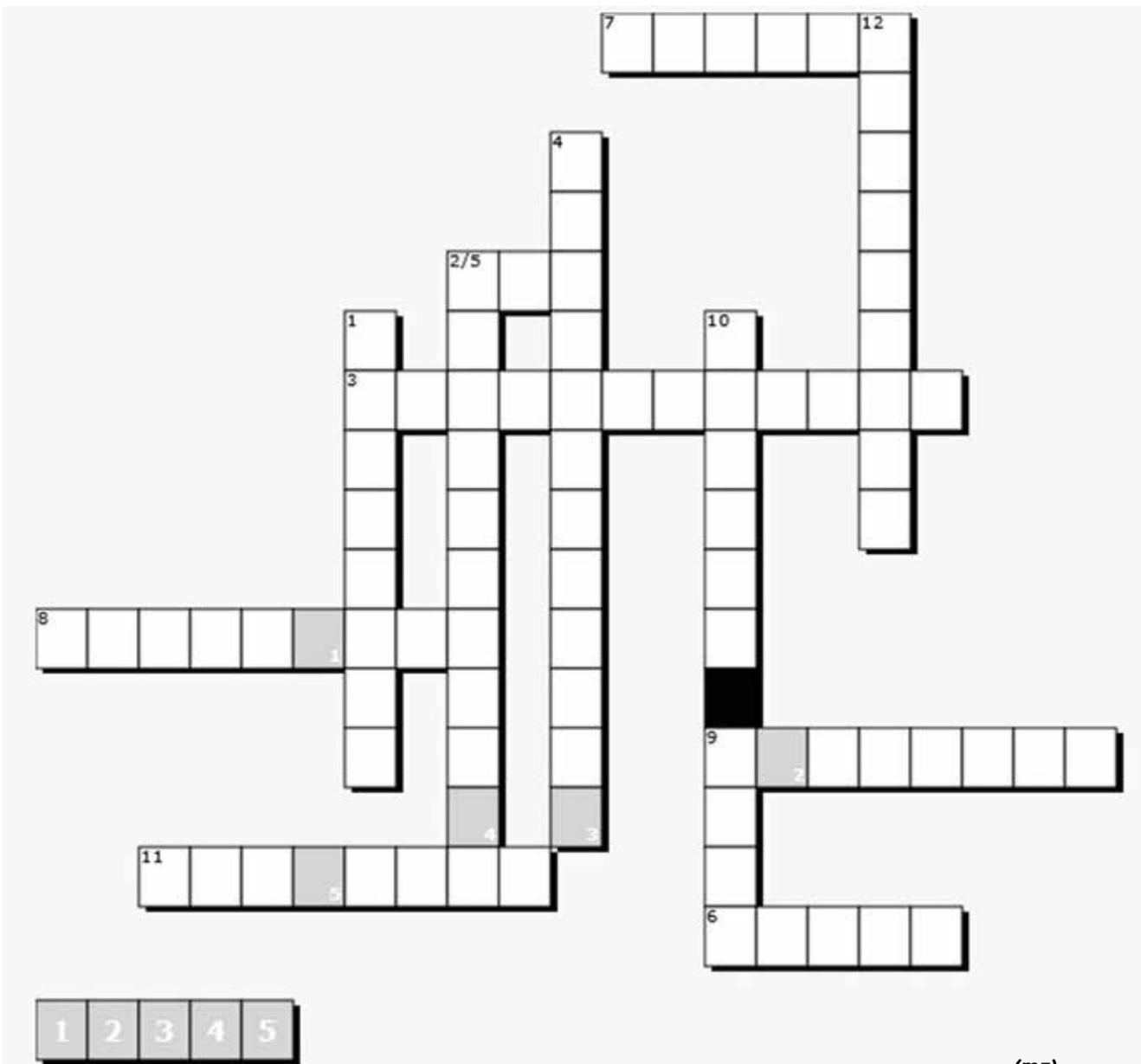
Do you also sometimes wonder about the simple neuroscientific questions in everyday life, but don't really feel like looking them up right away? For questions like this, **just mail us your question** (cns-newsletter@charite.de) and Dr. Harebrained will give us his explanation in the next issue! Our next issue's question: **Is it true that people born in summer need less sleep than people born in winter?**



Find out the correct answers. The boxes indicated make up the Mystery Word. Send the Mystery Word to cns-newsletter@charite.de to win **the book "Cantor's Dilemma"**. **Deadline: October 31, 2013.**

Please note that some answers consist of more than one word. In this case, an empty box should be used as a space.

1. Vitamin lacking in Wernicke-Korsakoff syndrome
2. One of the most promising treatments for stroke
3. Symptom in neuroleptic malignant syndrome
4. Condition that impairs short-term memory
5. Abbreviation for proteins involved in the modulation of the immune system by increased temperatures
6. Channel sensitive to temperatures below 28°C
7. ... perception is affected by hypothermia
8. Cold-related injury characterized by freezing of tissue
9. Peripheral cold injury that occurs in e.g. nose, ears, hands, feet
10. Condition caused by prolonged exposure to wet, but not freezing conditions
11. Mexican dish made of pork
12. One of the two nobel prize winners for studies of G-protein-coupled receptors



(mz)

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Orientation Week

The new junior students will be in Berlin soon and we are already excited! After the first day, Monday, September 30, of busy, administrative work, the program for the week lightens up. The first Wednesday in October is a day of celebration of both new and old, with the October 3 marks the anniversary of German reunification and we would like to do something special once again. As last year's "Walk the Wall" was a bit exhausting, this year aims for something different. We will keep you posted.

September	
1-4	KOSMOS Summer University 2013: "Human Sociality and the Brain. Decision Making in Social Contexts" (www.mind-and-brain.de/research/kosmos2013)
4-7	4 th European Students' Conference (http://www.esc-berlin.com/)
6-7	International Epilepsy Symposium: „New Insights into Epilepsy“
19-21	15. Hauptstadtkonress der DGAI für Anästhesiologie und Intensivtherapie (including a workshop on Neuromonitoring, http://www.hai2013.de)
October	
2	Graduation of the MSc students 2011-13: ceremony and reception, welcome party for new juniors
10-13	2 nd International Congress on Controversies in Stem Cell and Cellular Therapies (COSTEM) (http://www.comtecmcd.com/costem/2013/)
November	
8	Falling Walls Lab - Share your ideas in 3 minutes (http://falling-walls.com/lab/)
9	Falling Walls Conference (http://falling-walls.com/programme/)
11-13	1 st Annual Conference of the German Stem Cell Network (http://www.gscn.org/Conferences/2013/Home.aspx)
15-16	Neue Ansätze für die Therapie neurologischer Erkrankungen - Gemeinsames Symposium der Paul-Martini-Stiftung und der Leopoldina (http://bit.ly/1awL9SO)
20-22	Berlin Brain Days 2013 (http://neuroscience-berlin.de/bbd/)
December	
4-6	BSRT PhD Symposium - Regeneration is Communication: Fireside Chats between Cells & Matrices (https://www.bsrt-phdsymposium.de/)
March 2014	
21-25	International Congress of Clinical Neurophysiology
April 2014	
9-12	8 th International Symposium on Neuroprotection and Neurorepair (http://www.neurorepair-2014.de/)

Graduation

Similar to last year, this graduation of the 2011 cohort will take place during the Orientation Week on Wednesday, October 2. If you want to be the valedictory speaker, please contact the office. Feel free to join the ceremony as well as the party afterwards.

Berlin Brain Days 2013

The biennial Berlin Brain Days is back this year! The opening session will be on Wednesday, November 20 at the Humboldt University, Campus Nord, Building 2. Begin: 6pm. Be sure to submit your talk or poster presentation until September 30. Active participation yields two ECTS credit points (MSc and PhD alike). More on the event and registration at <http://neuroscience-berlin.de/bbd/>.

New PhD Students

The program warmly welcomes our most recently admitted doctoral students: Valérie Boujon (AG Kronenberg) and Andreas Horn (AG Kühn), who applied for the usually less popular May application deadline and were admitted after their exam on July 24 admitted them.

Neurasmus Students

The first cohort of the 2011 Neurasmus students will graduate this August in Bordeaux. Congratulations from Berlin! The 2012 students have left Berlin and are already in their second European country - Amsterdam, Bordeaux, or Coimbra.

Imprint

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