**Briefing Paper**

**mbr63 (Mangesh Raut)**

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**A daily temperature rhythm in the human brain predicts survival after brain injury.**

Rzechorzek, N. M., Thrippleton, M. J., Chappell, F. M., Mair, G., Ercole, A., Cabeleira, M., CENTER-TBI High-Resolution ICU (HR ICU) Sub-Study Participants and Investigators, Rhodes, J., Marshall, I., & O'Neill, J. S. (2022). A daily temperature rhythm in the human brain predicts survival after brain injury. Brain: a journal of neurology, awab466. Advance online publication. <https://doi.org/10.1093/brain/awab466>

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Abbreviations: BMI = body mass index; CBF = cerebral blood flow; CENTER-TBI =Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury; TBI=traumatic brain injury; MRS=magnetic resonance spectroscopy; MSFsc = sleep-corrected midpoint of sleep on free days; TBo = body temperature; TBr = brain temperature; TTM = targeted temperature management

Brain temperature (TBr) is rarely measured directly since invasive methods are required. Abnormal temperatures have been recognized as a sign of disease for more than two millennia. Brain cell function is unequivocally temperature-dependent, and its relationship to body temperature is well understood. The application of targeted temperature management (TTM) in neurocritical care remains highly controversial. Despite its irrefutable clinical value, the normal range of human TBr is unknown. Several lines of evidence suggest that healthy TBr may vary over time and between brain regions. Deviations from TBo may have transformative diagnostic and/or prognostic utility for acute and chronic brain disorders. Spatially resolved TBr data can now be obtained non-invasively. In non-human primates, deep brain structures are warmer than the surface.

Brain thermometry has proven to be a powerful research application of MRS. We hypothesized that healthy human TBr would be very diurnally (in the manner expected for a daytime active mammal) and that disruption of daily temperature variation would be associated with an outcome after traumatic brain injury (TBI). Patients undergo interventions to achieve a "normal" brain temperature. We aimed to determine the clinical relevance of brain temperature in patients. Patients' brain temperatures (n = 114) ranged from 32.6 to 42.3°C, with the mean temperature exceeding body temperature (37.5°C). Brain temperatures in healthy participants ranged from 36.1 to 40.9°C; the mean brain temperature exceeded the oral temperature (36.0 0.5°C). Aging by 10 years increased the odds of death by 11-fold, and lack of daily brain rhythm increased the risk of death in intensive care by 21-fold. A warmer mean brain temperature was associated with survival, however, and aging by 10 years increased the odds of death 11-fold (P = 0.0002). We conclude that daily rhythmic brain temperature variation may be one way in which human brain physiology may be distinguished from pathophysiology.

Human brain tissue functions normally at temperatures 1-3 degrees Celsius higher than previously thought. Daily TBr rhythm is associated with a 21-fold increased chance of survival after brain injury. Future studies should address whether supporting normal TBr variation is beneficial to patients. The highest temperature ever measured in a healthy individual was 40.9°C in the thalamus of a luteal female in the afternoon. There is no direct evidence that a TBr of this magnitude would cause brain damage, and similar deep brain temperatures are physiologically observed in other mammals. The TBr range in our volunteers raises doubt over whether TBr was abnormally high in some patient reports. Whether adults should be cooled at all in neurocritical care is still debated. A clear understanding of how and why TBr varies in health and disease is imperative. Time-based human neuroimaging studies are sparse, but some morning/afternoon comparisons are consistent with diurnal regulation of brain morphometry as well as diurnal variation in neural activity and metabolism. Prior studies were underpowered without consideration of chronotype and a late evening time point.

Our results offer compelling evidence of a daily temperature rhythm throughout the normal human brain. A limitation of our design is that data could not be collected at the predicted TBr nadir during sleep. Crucially, our robust statistical approach caters to multiple physiologically relevant confounders within and between individuals. The brain is an "open" thermodynamic system, performing no mechanical work. It releases heat at 0.66 J/min/g of tissue, which is primarily removed by CBF. Regional variation in neurovascular anatomy plays a chief role in creating spatial TBr gradients. The lower temperature of the hypothalamus might reflect its closer proximity to major vascular networks such as the Circle of Willis. Although not possible within the time constraints of our scanning protocol, arterial spin labeling could be used to confirm spatiotemporal relationships between TBr and CBF. In principle, technical limitations could potentially exaggerate MRS-derived temperature differences at the extreme edges of regions of interest (cerebral layer Sup4). The spatial distribution we have found is, however, very similar to non-human primates, excepting a larger gradient magnitude.

We do not assume that temperature should be homogeneous across brain regions or between different tissue types within the brain. We did not apply a post-acquisition correction to our MRS data to equalize temperatures between grey and white matter, since this would overlook the clear tissue temperature differences observed in non-human primates and human brains. An increase in mean TBr and a trend upwards in minimum TBr with age suggests that overnight brain cooling becomes less efficient in older people, leading to a damped TBr rhythm. Age-dependent reduction in the TBr range (and thus amplitude) is consistent with studies of TBo. Cerebral blood supply is considered so efficient that heat removal is achieved without the need for other mechanisms under most circumstances. However, literature linking neurodegeneration to cerebrovascular compromise indicates that our key brain cooling mechanism progressively deteriorates with age. The findings suggest that age is an important factor to consider when interpreting TBr data in humans. Neuronal activity is highly sensitive to temperature change, although this is generally considered to be most problematic in the acute setting. Given that cooling can terminate epileptic discharges, diurnal changes in TBr may well contribute to the diurnal variation in seizures and cluster headaches.

Human brain temperature research has previously depended on data collected from brain-injured patients in intensive care when direct brain monitoring is frequently required. Researchers have recently been able to quantify brain temperature in healthy people using a brain-scanning technology called magnetic resonance spectroscopy (MRS). However, until today, MRS had not been used to investigate how brain temperature changes during the day or how an individual's "body clock" influences this. The first 4D map of healthy human brain temperature has been created by researchers at the Medical Research Council (MRC) Laboratory for Molecular Biology in Cambridge, UK. This map reveals the surprising extent to which brain temperature changes by brain area, age, sex, and time, which defies various earlier notions of the day. These findings also cast doubt on the generally held idea that the human brain and body temperature are identical.

The study, which was published in the journal Brain, also looked at data from traumatic brain injury patients and found that the presence of daily brain temperature cycles is highly linked to survival. These discoveries could help to improve brain injury diagnosis, prognosis, and treatment. The researchers enlisted 40 volunteers, ages 20 to 40, to be scanned at the Edinburgh Imaging Facility, Royal Infirmary of Edinburgh, in the morning, afternoon, and late evening for one day to examine their healthy brains. They also gave the participants a wrist-worn activity monitor, which allowed them to account for genetic and lifestyle variances in the timing of each person's body clock, or circadian rhythm. The biological time of day that each brain temperature measurement was collected allowed variances in each volunteer's body clock to be factored into the study for both "night owls" and "morning larks." The optimal brain temperature, type of cooling device, and strategy for the rewarming phase still need to be clarified. Maintaining normothermia and avoiding hyperthermia are both beneficial in TBI patients. Early induced hypothermia at the craniectomy region may be a promising strategy for severe TBI patients.

The results of this systematic review show that core body temperature (measured at various sites of the body) is not a reliable 'proxy' for brain temperature in patients with severe TBI. Hence, the use of body temperature to predict brain temperature is not advisable in the clinical setting. Direct brain measurement is still the best way to monitor brain temperature in patients with severe traumatic brain injury. A healthy human brain can achieve temperatures that would be considered feverish elsewhere in the body. Such high temperatures have been measured in people with brain injuries, but they were considered to be the outcome of the injury. The temperature of your brain reduces before you go to sleep at night and rises during the day. Scientists have created the most complete examination of normal human brain temperature to date. Daily brain temperature rhythm is significantly linked to TBI survival. This paves the way for future studies into whether daily brain temperature disruption might be used as an early indicator for a variety of chronic brain illnesses.

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