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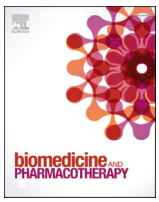

Review

# Brain temperature in healthy and diseased conditions: A review on the special implications of MRS for monitoring brain temperature

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ABSTRACT

Brain temperature determines not only an individual's cognitive functionality but also the prognosis and mortality rates of many brain diseases. More specifically, brain temperature not only changes in response to different physiological events like yawning and stretching, but also plays a significant pathophysiological role in a number of neurological and neuropsychiatric illnesses. Here, we have outlined the function of brain hyperthermia in both diseased and healthy states, focusing particularly on the amyloid beta aggregation in Alzheimer's disease.

## 1. Introduction

Regional brain temperature measurement is novel method that yields pathophysiological insights and associated therapeutic opportunities for a neuroprotective approach to degenerative diseases [1]. Monitoring regional cerebral temperature has not yet been found to guide goal-directed cerebral protection. However, this is due to the lack of reference data regarding the application of targeted temperature management associated with the difficulty of collecting data through invasive direct measurements [1,2]. Previous studies have employed noninvasive techniques such as magnetic resonance imaging and spectroscopy, infrared spectroscopy, microwave radiometry and ultrasound thermometry to determine the temperature of the brain [3]. Neural temperature measurement sensors are another feasible, noninvasive option. For instance, thermocouples, resistance temperature detectors (RTDs), and semiconductor-based optical sensors are all noninvasive implantable temperature monitoring devices, although they have not yet been used on humans due to concerns about potential side-effects [3]. Figs. 1, 2 Table 1.

In addition to offering the new therapeutic insights described above, recent studies suggest that deviations in brain temperature may also be of diagnostic value in neurological disorders in the clinical setting [4–9], although a clear dissociation of these deviations from healthy physiological variations over time is essential [9]. The major error here seems to involve an assumption of brain temperature based on body core, which leads to the neglect of the pathophysiological importance of brain-specific regions. Several studies have suggested that brain cell function is highly dependent on temperature, as suggested in conditions in which the brain temperature of brain-injured patients was found to be significantly increased using intracranial probes allowing direct, but invasive, measurement from a single cerebral locus [10]. In contrast to these invasive approaches, magnetic resonance spectroscopy (MRS) may offer an alternative monitoring system in which spatially resolved brain temperature data can be obtained noninvasively [1,2]. A recent study by Thrippleton et al. evaluated the feasibility of using MRS to measure brain temperature and mapping, and described it as a reliable method, especially at 3 T [1].

In this setting, the mechanism by which regional temperature is measured involves the temperature-reliant chemical shift of water in contrast to the reference metabolite n-acetyl aspartate (NAA), which is not temperature-dependent [11]. Temperature measurement and monitoring based on the water proton chemical shift is divided into two different imaging techniques - spectroscopic imaging and the phase mapping method, which is more commonly used. Based on this method, brain temperature for each cerebral tissue voxel can be calculated using a formulation between the above parameters, as described in a recent study. In brief, such a rational approach yields a mathematical value for the difference in chemical shift between water and NAA, thus providing an estimated value for brain temperature in healthy subjects [1,11].

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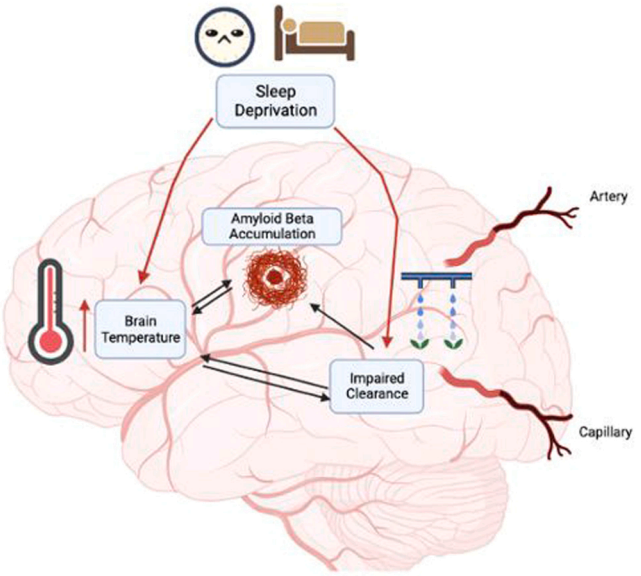


**Fig. 1.** [38] The vicious circle between increased brain temperature, sleep deprivation, impaired brain clearance, and amyloid beta accumulation.

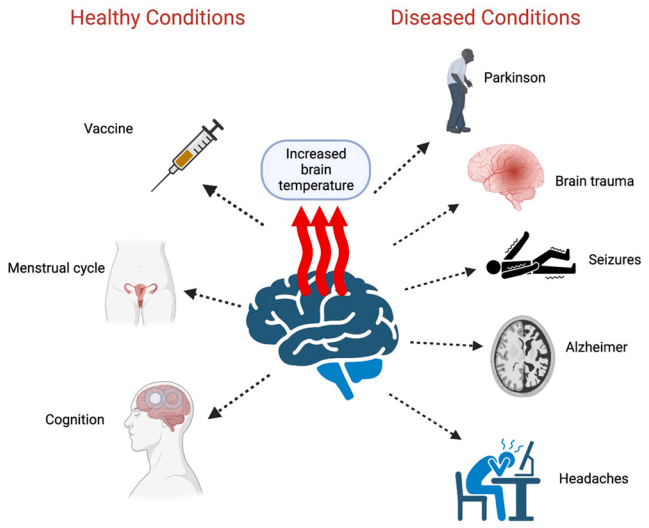


**Fig. 2.** Graphical Abstract:[38] Conditions that increase brain temperature.

**Table 1**
Invasive and noninvasive techniques used for monitoring brain temperature[3].

| Noninvasive Techniques | Invasive Techniques |
|---|---|
| Neural temperature measurement sensors<br>• Thermocouples<br>• Resistance temperature detectors (RTDs)<br>Optical temperature sensors (e.g. optoacoustic/ photoacoustic)<br>• Thermistors<br>• Semiconductor-based sensors<br>Temperature measurement instruments<br>• Infrared Thermography<br>• Infrared Spectroscopy<br>• Magnetic Resonance Spectroscopy<br>• Ultrasound Thermometry<br>• Microwave Radiometry | Temperature measurement instruments<br>• Probe-based monitoring<br>• Implantable sensors |

## 2. Brain temperature in healthy and disease conditions

### 2.1. Brain temperature in healthy individuals

The average brain temperature in healthy individuals is more than two degrees higher than that of the body core, depending on factors such as the time of day, the brain region involved, sex, menstrual cycle, and age [2]. A similar difference can be observed at night, when cerebral blood flow peaks [13]. This is principally mediated by intact cerebral perfusion, a compensatory mechanism especially effective in young, healthy brains. It is therefore physiologically plausible that lower temperature values may be observed for specific brain regions (i.e. the hypothalamus) which are closely associated with major vascular structures, such as the Willis Circle [2,12,14]. This suggests the importance of intact neurovascular integrity for an effective heat-removal mechanism by creating spatial gradients in brain temperature. It is also worth mentioning that yawning and stretching are compensatory thermoregulatory mechanisms against increased brain temperature mediated by various neurotransimitters such as acetylcholine, serotonin, dopamin and GABA [35,36]. This is suggested by the same authors showing that heavy nasal breathing terminated the yawning reflex by reducing the brain temperature [37].

Based on these physiological data, it is not unreasonable to assume that recent research has associated increased brain temperature with a less efficient overnight cooling mechanism in the brains of older individuals [12–14]. This might open a new window into the possibility of whether such a mechanism may contribute to diseased conditions in the brain, regardless of the kind of impairment, such as an apoplectic character, as in neurovascular diseases, or a relatively slower progression in degenerative neurological disorders.

Another interesting subject is that elevated brain temperatures have been measured following vaccine administration [15]. Plank et al. hypothesized that an increase in brain temperature should occur due to neuroinflammation following typhoid vaccine administration [15]. That study suggested that peripheral invasive procedures may affect the central nervous system, another important subject requiring further analysis.

Entropy is another factor shown to be closely associated with brain temperature. Entropy is classically defined as a thermodynamic quantity expressing a system's inability to convert thermic energy to mechanical work, in other words, a degree of disorder or randomness in the system. Heat causes greater randomness if added to a system and thus higher entropy, indicating a relationship between increased brain temperature and higher brain entropy. One good example of this is an interesting recent study by Saxe et al., who investigated the relationship between intelligence and brain entropy using resting-state fMRI of healthy adults. Those authors observed a positive association between cognitive scores and brain entropy, especially in the prefrontal cortex, inferior temporal lobes and cerebellum [16]. This suggests that increased entropy derived from complex behavioral performance and intellectual capacity might theoretically increase the temperature of the brain. However, similar to other biological systems, this association might be true to some extent, and it is still unclear whether a process going beyond this fine line may induce or be related to disease conditions, indicating that further mechanistic studies are needed to shed light on this chicken and egg paradox.

### 2.2. Brain temperature in disease conditions

Measuring the brain temperature of a patient with neuronal damage is exceptionally useful for physicians in terms of understanding the effects of that damage and the healing process as well as the post-surgery also the post-surgery recovery mechanism [3]. Neuronal activity is highly sensitive to temperature differences, and the brain represents an open thermodynamic system characterized by aerobic metabolism releasing a significant amount of heat [12]. Several studies monitoring

focal central pathological processes have suggested that increased brain temperature coincides with inflammatory and metabolic responses of the central nervous system, including some neurological diseases, revealing a considerable contribution of increased brain temperature to the incidence of seizures, cluster headaches, brain trauma, and cerebrovascular diseases [13,17,18].

For instance, Lu et al. studied the prognostic value of postoperative diurnal brain temperature in patients with intracranial hemorrhage and reported that brain temperature may be capable of predicting the recovery process and constituting a prognostic mortality marker [19].

This is confirmed by stroke and traumatic brain injury patients exhibiting elevated brain temperature in contrast to core body temperature, suggesting a possible role of mild hypothermia as a novel therapeutic option for stroke patients, since intranasal cooling can be easily and noninvasively (intranasal cooling) applied [20]. Consistently, most seizures peak in the morning, when brain temperature is increased, and can be eliminated with cooling strategies [21].

Previous studies considering neuroinflammation as a pathogenetic factor in psychiatric disorders have shown differences between schizophrenia and bipolar disorder in terms of thermoregulation. Other studies comparing healthy individuals with patients with neuropsychiatric conditions have shown that there is a thin line between some neuropsychiatric conditions, such as schizophrenia, in which the physiological correlation between glutamate and brain temperature was lost in the anterior cingulate gyrus but remained negative in healthy subjects [22]. This is in good agreement with a recent study showing a clear correlation between schizophrenia and brain temperature, which was significantly elevated.

Parkinson's disease is known to be caused by several factors, such as neuroinflammation and increased oxidative stress [23]. A recent study showed increased temperature in patients with Parkinson's disease due to inflammatory factors in the acute stages followed by a considerable decline due to impaired mitochondrial biogenesis (mitobiogenesis) [23] as the disease progressed. This is in line with previous data for higher brain temperature in the hypothalamus, posterior cingulate gyrus, centrum semiovale, and lenticulate nucleus in early onset Parkinson's disease than in healthy individuals [24].

## 3. The special implication of brain temperature in Alzheimer's Dementia

As described above studies involving both animal and human models have reported elevated body core and brain temperatures in acute neurological injuries, which aggravate neuronal damage [25]. It is therefore not surprising that recent research has associated increased brain temperature with a less efficient overnight cooling mechanism in the brains of older individuals [12–14].

However, the critical issue here is whether sleep deprivation and age-related progressive deterioration of brain-cooling mechanisms may alter the molecular clearance of abnormal proteins from the brain in a manner capable of initiating a neurodegenerative process. These studies are notably consistent with the recent literature showing that body temperature may contribute to disrupted sleep patterns in patients with dementia. For example, recent evidence has shown that brain regions with peak temperatures were also those most affected by clearance deterioration after sleep deprivation [26]. This suggests that impaired daily brain temperature regulation induced by sleep deprivation and aging may contribute to the aggregation of abnormal proteins in neurodegenerative diseases.

Alzheimer's disease is characterized by several irregular protein modifications, including abnormal modification of amyloid precursor protein (APP) and tau, leading to toxic aggregates. Among these, amyloid β (Aβ) fibrils are especially sensitive to heating, consistent with the previous literature concerning enhanced intracellular protein immunoreactivity under increased thermogenesis conditions [27]. In association with this, temperature-dependent conformational changes observed in specific A beta epitopes reveal a vicious cycle between impaired thermoregulation and the accumulation of Alzheimer's disease neurons in Alzheimer's-like neuropathology. In this context, in vitro calorimetric measurements show that Aβ42 is a heat-releasing process that is absorbed by the cell. This occurs in such a manner that increased intracellular temperature leading to the disturbance of critical energetic structures may additionally raise the intracellular temperature, facilitating secondary accumulation of temperature-sensitive intracellular proteins, thus forming a vicious cycle [28,29]. These findings support the general concept that thermogenesis is closely linked to cellular stress, and that these processes together may promote abnormal protein aggregation. Similar to healthy conditions, entropy has also been of considerable interest in the context of Alzheimer's disease. For instance, Wang et al. assessed brain entropy mapping comparing healthy aging and Alzheimer's disease and observed time-dependent entropy increases in both. However, in the severe stage of Alzheimer's disease, entropy tends to decrease due to amyloid beta aggregation and related perfusion deficits, while continuing to increase in normal aging [30]. These findings fit well with the unique thermodynamic features of the beta amyloid growth process that is highly dependent on a nucleation-elongation model associated with a high energy blockage. It is thus reasonable to assume that some localized energy-intensive areas, characterized by aging or stressed cells during cellular stress, may represent core areas for the initiation of nucleation and subsequent elongation of abnormal amyloid aggregation leading to numerous entropic alterations attributed to different stages of neurodegenerative disease. Strong evidence for this hypothesis was provided by a very recent novel study by Chung et al., who evaluated amyloid beta aggregation under increased temperature conditions by directly calibrating temperature in an intracellular manner [31]. The findings of that study supported the idea that Aβ42 elongation is directly responsible for increasing cell temperatures by leading to the formation of Aβ42. It did this by exceeding the energy threshold for subsequent accumulation processes, quickly establishing a vicious circle between the thermogenesis effect and protein aggregation.

In clinical terms, considering the accumulating data for patients with Alzheimer's disease with impaired core body temperature rhythms, it may be interesting to evaluate the potential neuroprotective effects of hypothermia in dementia. However, the findings of several studies [32,33] indicated that low body temperature led to a reduction in glucose metabolism, which ultimately exacerbated the neurodegenerative process in Alzheimer's disease. Furthermore, a number of in- vivo and in-vitro studies have observed deleterious effects of hypothermia on protein aggregation [34]. The cumulative effect of these findings was to halt the growing interest in the role of hypothermia in Alzheimer's disease. Nevertheless, since entropic changes and associated brain temperature alterations follow a U-shaped pattern, indicating increased brain temperature due to prominent neuroinflammation in the early stages of Alzheimer's disease, reducing the temperature of the brain may be particularly beneficial in the early stages of the neurodegenerative process. To the best of our knowledge, however, no previous studies have investigated the efficacy of a time-specific hypothermic approach in the treatment regimen in Alzheimer's disease.

## 4. Translation outlook

To summarize, the significant susceptibility of neuronal activity to temperature suggests that the brain should be isothermal, but data collected from human and animal subjects show spatiotemporal variation [2]. In other words, brain temperature determines an individual's intelligence and behavioral capacity, as well as the prognosis and mortality rates of many brain diseases. In addition to changing in response to various physiological events, such as normal aging and receiving of vaccines, brain temperature also seems to play a critical role in pathophysiological processes in different diseases such as brain trauma, acute neurological injuries, and neurodegenerative and psychiatric diseases. In light of all this evidence, it is crucially important to measure brain temperature for a better understanding of the pathophysiology of neurodegeneration. Although the MRS method may involve some patient-dependent calculation errors, such as tissue susceptibility changes and body movements [35], it can still represent a unique noninvasive diagnostic alternative for measuring and monitoring brain temperature in healthy and disease conditions.

## CRediT authorship contribution statement

**Burak Yulug:** Conceptualization, Writing – review & editing. **Halil Aziz Velioglu:** Supervision, Writing – review & editing. **Dila Sayman:** Writing – original draft, Writing – review & editing, Investigation, Visualization. **Lutfu Hanoglu:** Supervision.

## Conflict of interest statement

We declare that we have no known financial interest or any relationships that could have to affect the work reported in this paper.

## Data Availability

Data will be made available on request.

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