Time-Dependent Relationships Between Human Brain and Body Temperature After Severe Traumatic Brain Injury

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Abstract: There is uncertainty about the reliability of using body temperature readings as a 'surrogate' measure of brain temperature.

Aim: To determine the temporal inter-relationship between body and brain temperature after severe traumatic brain injury (TBI).

Setting and Patients: Large University teaching hospital in the North West of England. Patients admitted for emergency neurocritical care. All patients received dual-modality monitoring of brain tissue pressure and temperature *via* invasive intracerebral micro-sensors. Body temperature was measured using an indwelling thermistor inserted in to the rectum.

Methods: Temperature was monitored continuously with values stored to a bedside data acquisition system at intervals of 10 minutes. Data were transferred to a spreadsheet at end of each individual's monitoring period for further analysis under Matlab routines. The method of functional principal components was used to determine the time-dynamics of brain and body temperature relationships.

Results: In the period after severe TBI, median body and brain temperature for all readings and in all patients was 37.6^{o}C and 37.7^{o}C respectively; a statistical ($p < 0.001$) but not clinically significant difference. A strong regression relationship between brain and body temperature was demonstrated (functional coefficient of determination, $R^2 = 0.7623$, $p < 0.0020$).

Conclusions: Body temperature is a good early predictor of brain temperature but only during the first two days after severe TBI. The results will be of value for future predictive modeling of brain temperature changes, particularly where brain tissue monitoring is not clinically justified or available. In particular, results demonstrate the uncertainty in using body temperature as a surrogate for brain temperature beyond the first two days after severe traumatic brain injury.

Keywords: Brain trauma, brain temperature, body temperature, time-dynamics, functional principal component, functional regression.

INTRODUCTION

Despite wide variations in climatic conditions, body temperature in homoeotherms remains relatively constant [1]. The human physiological temperature range is narrow and varies by 3-4^{o}C only, above or below 37^{o}C [2]. In hospital patients, by far the more common manifestation of disturbances in thermal homeostasis is a rise in body temperature, typically due to fever [3]. Fever is characterized on the basis that the thermoregulatory 'set-point' [4] rises above 'normal', not as a result of excessive external heat load as occurs in heat stress and heat stroke but due to release of inflammatory molecules and mediators driving endogenous heat production [5] until a new thermal 'steady state' is reached. It seems however that there is a 'ceiling' above which a rise in body temperature is no longer under central control, for it has long been held that body temperature in excess of 106^{o}F (41.1^{o}C) is rare [6]. For body temperature in excess of 40-41^{o}C, heat stress and heat stroke [7] should be suspected.

Although the biological response to bacterial and cell-derived 'pyrogens' is metabolically costly, the customary view is that fever, with its long evolutionary history, probably has an adaptive role in host defense against infection and is broadly a protective biological response [8]. By contrast, when damage to the brain occurs, the impact of a rise in local temperature is a rather more controversial issue [9]. Whilst the prevailing view is that even small increases (1-2^{o}C) in brain temperature accelerate damage to brain cells [10] (and consequently a worse outcome for the patient) this view is not wholly supported. Recent data from our group [11, 12] suggests that whilst raised brain

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temperature is common, it is not a predominant factor in poor outcome; other, as yet undetermined factors, are likely involved [12]. However, since the precise impact of altered brain temperature on a) metabolic and inflammatory cascades and b) neurological and functional outcome remains uncertain, measurement of local tissue is warranted especially in view of the difference in temperature readings between brain and body measurement sites that occur in some patients and at some times [13].

It is for this reason that we remain uncertain as to whether body temperature performs as a consistently reliable surrogate for brain temperature. With the possibility of understanding the dynamics between brain and body temperature, there comes the potential for modeling time-dependent changes of brain temperature from body temperature and *vice versa*. The aim was to undertake a prospective observational cohort study to determine the temporal inter-relationship between body and brain temperature. The results will be of value for future predictive modeling of brain temperature changes in patients for whom invasive brain tissue monitoring is not justified on clinical grounds.

METHODS

Patients

Intracerebral pressure (ICP) monitoring is now a guideline recommendation from the Brain Trauma Foundation for patients with severe TBI [14]. Patients admitted to our Regional Centre at Salford Royal NHS Foundation Trust (Hope Hospital) for neurocritical care and who required invasive intracerebral monitoring on clinical grounds were eligible for inclusion in the study. Data from two separate cohorts recruited during 2005-2006 and 2007-2008 were collected from patients with severe TBI. The research was carried out in accordance with the Declaration of Helsinki (2008) of the World Medical Association and was approved by the local Research Ethics Committee.

The technique for insertion of dual-modality brain sensors, measuring ICP and temperature and deep body (rectal) temperature are described elsewhere [11, 12]. Briefly the brain microsensor was inserted shortly after arrival of the patient to the ICU, using Camino 110-4BT (Integra Neurosciences, Andover UK) and Raumedic Neurovent-PTemp™ (Raumedic AG, Munchberg, Germany) sensors respectively for studies between 2005-2006 and 2007-2008. Continuous monitoring of brain and body temperature readings were obtained alongside routine clinical monitoring. Temperature readings were displayed *via* a bedside data acquisition system and at intervals of 10 minutes. All data were stored to a personal computer (PC) at the bedside and extracted later to an Excel spreadsheet (Microsoft Corporation).

Mathematical Modeling Using Functional Regression

Functional data can be represented through functional principal component [17]. Assume that the random predictor $X(s)$ and response $Y(t)$ functions are squared integrable with domains S and T, respectively. One can use the method in [27] to expand both trajectories X and Y as follows,

$$X(s) = \mu x(s) + \sum_{j=1}^{\infty} \xi_j \phi_j(s), \quad (1)$$

$$Y(t) = \mu_Y(t) + \sum_{k=1}^{\infty} \zeta_k \psi_k(t), \quad (2)$$

Where $\mu_X(s)$ and $\mu_Y(t)$ are the mean functions; ξ_j and ζ_k are random coefficients centered at zero that are called functional principal component scores; ϕ_j and ψ_k are the sequences of basic functions, for which eigenfunctions are the common choices [27].

The functional linear regression model [15] with smooth response function $Y(t)$ and smooth predictor function $X(s)$ is as below,

$$E(Y(t)\big|X) = \mu_{Y(t)} + \int_s \beta(s,t) X^c(s) ds, \quad (3)$$

where $X^c(s) = X(s) - \mu_{X(s)}$ and $\beta(s,t)$ is the bivariate regression function which is assumed to be smooth and square integrable, i.e., $\int_T \int_S \beta^2(s,t)\, ds\, dt < \infty$. The two-dimensional function $\beta(s,t)$ characterizes the dynamical relation between the response function $Y(t)$ and predictor function $X(s)$, which can be estimated from the data using certain statistical techniques [15].

All data are calculated using Matlab (ver 7.12, R2011a) and software package PACE (principal analysis by conditional expectation) version 2.14 [http://anson.ucdavis.edu/~ntyang/PACE/]. For the interested reader, a detailed description of the methodology of functional regression analyses can be found elsewhere [15].

Briefly, the functional linear regression method is an extension of a traditional linear regression model used

here because repeated longitudinal measurements for both outcome and explanatory factor are taken on a large number of occasions for different lengths of time. In essence, this is a two-stage procedure. First, the outcome and explanatory variables are summarized by their principal component scores [16,17]. Secondly these scores are regressed on each other to estimate a two-dimensional parameter, Beta, describing the longitudinal relationship [15].

RESULTS

Patient Demographics

Fifty patients, 37 male, aged 16 to 75 (median 32) years with a baseline Glasgow Coma Score (GCS) of 3-14 (median 5) were included in the study. With the exception of two patients whose brain and body temperature monitoring commenced three and five days after injury, monitoring commenced either on the day of injury (n=26) or on the following day (n=22). Since the functional linear regression method enjoys the property of dealing with unbalanced longitudinal data, all patients' data are used in our analysis so that no information is lost in the statistical modeling for the data. The most common cause of brain injury was due to road traffic accident (n=21 42%) and falls (n=21 42%) with a smaller number due to assault (n=6 12%) gunshot (n=6 12%) and traumatic haemorrhage (n=1 2%). Brain and body temperature 'pairs' were recorded every 10 min for a duration of 1-12 (median 3.5 days).

Temperature Readings

The number of measurements of brain and body temperature readings for each of the 50 patients ranged from 69 to 1516 (median 373.5) creating a mass of data points and making it difficult to distinguish the profiles of individual data sets. The individual data points for brain and body temperature for the study patients are shown before (Figure **1**) and after (Figure **2**) removal of 'unphysiological' values (Figure **2**).

Missing Data

Missing data were evident in all data sets and typically due to a) data storage errors b) sensor disconnection during the course of clinical care [18].

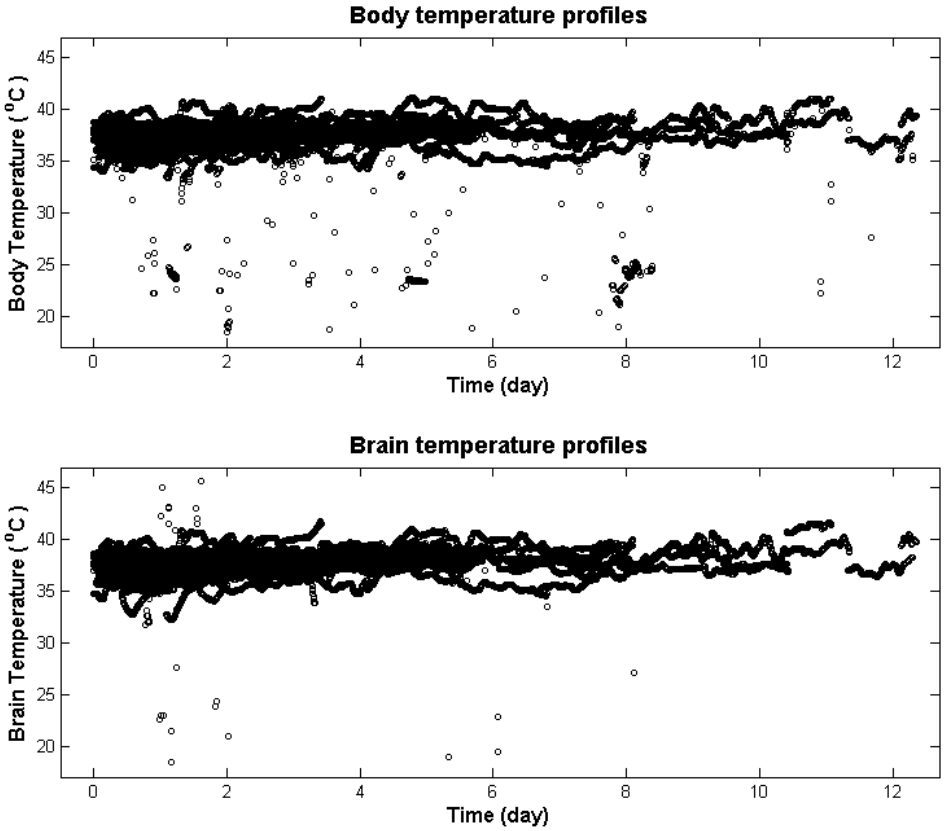

Figure 1: Plot of the observed raw data for body and brain temperature. Upper panel, body temperature (^{o}C) measurements for all patients (n=50) plotted against time (days after TBI). Lower panel, brain temperature (^{o}C) measurements for all patients (n=50) plotted against time (days after TBI). Each circle represents a single body (or brain) temperature reading taken at intervals of 10 minutes for the duration of each patient's study period.

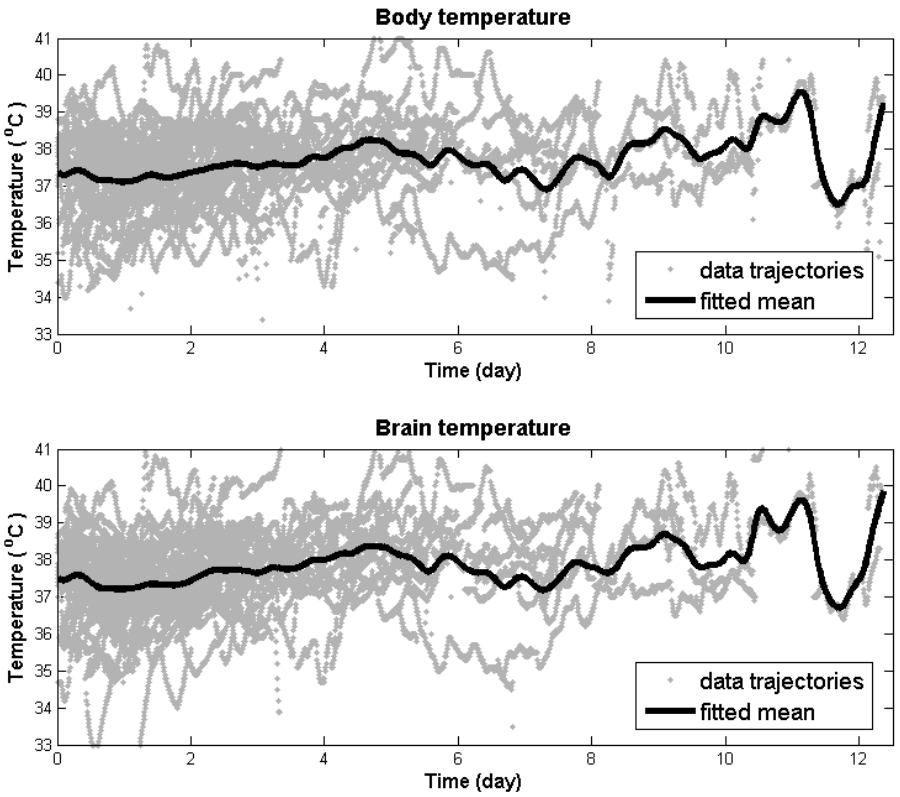

Figure 2: Plot of body and brain temperature data (grey dot) after removal of 'unphysiological' values with their smooth estimates of mean functions (thick solid line in each panel) superimposed on temperature data points.

Preliminary data processing was conducted to remove unpaired temperature values. For example, where a single temperature value was evident in the data (but the corresponding brain temperature or body temperature value was missing) such incomplete pairs were removed and considered as 'missing'. Missing values occurred in 4-34% (median 30%) of the temperature datasets. Temperature extremes i.e. 'unphysiological' values were evident and likely due to readings artifact especially with respect to rectal temperature values (Figure **1**, upper panel). Since therapeutic hypothermia was not instituted at this Centre, data were deleted at values below 33^{o}C on the basis that the value was unreliable (primarily for rectal measurements). High temperature values (>41.0^{o}C) were also deleted. After this preliminary data processing, the individual temperature recordings ranged from 33.4-41.0^{o}C (median 37.6^{o}C) and 33.0-41.0^{o}C (median 37.7^{o}C) for body temperature and for brain temperature respectively. An example of the temporal profile of brain and body temperature of two 'typical' severe TBI patients is illustrated in Figure **3**.

Mathematical Modeling

After data cleaning, estimates of the mean temperature functions (Figure **2**) show that the mean pattern for both body and brain temperature is similar. With a functional coefficient of determination, R^2 =0.76 (p = 0.002) a strong regression relationship is apparent. Figure **4** provides a visualizing tool to assess the relationship between the body and brain temperatures that changes over time. One of our primary aims was to predict the response function (brain temperature) by the predictor function (body temperature). In the view of Equation (3), one could obtain the predication of the response function *via* the conditional expectation. In practice, the Beta function $\beta(s,t)$. can be interpreted as a weight which tells us how much contribution the body temperature on a specific day has towards the brain temperature on a specific day. For example, if we are interested in brain temperature on day 2, we may use all the information of body temperature measurements collected up to that day to predict brain temperature on day 2 by functional linear regression model. Hence, with reference to the Beta parameter function (Figure **4**) the prediction of brain temperature from body temperature can be determined. The key information provided by the Beta function is that the clinician may predict one's brain temperature in the future based on one's body temperature on the previous days. For example, if one knows that there is a very strong positive association

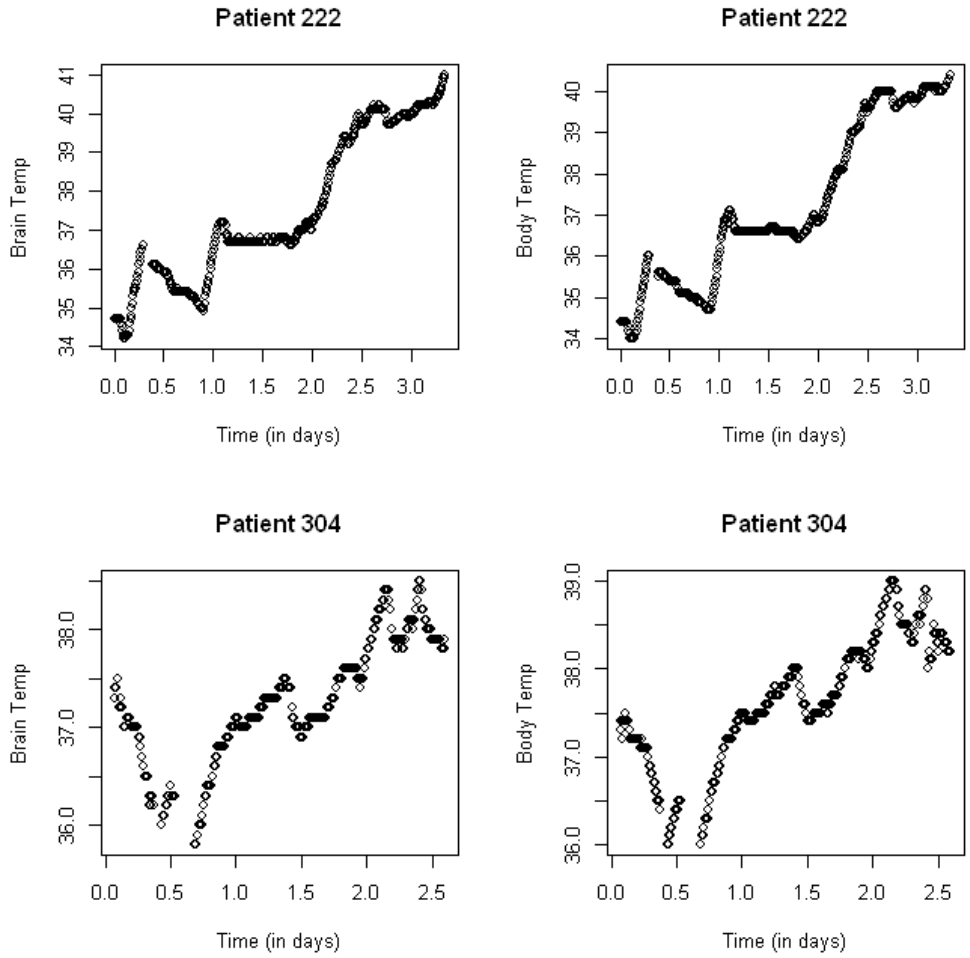

Figure 3: Examples of two randomly chosen patients' temperature profile (brain and body) over the course of the study.

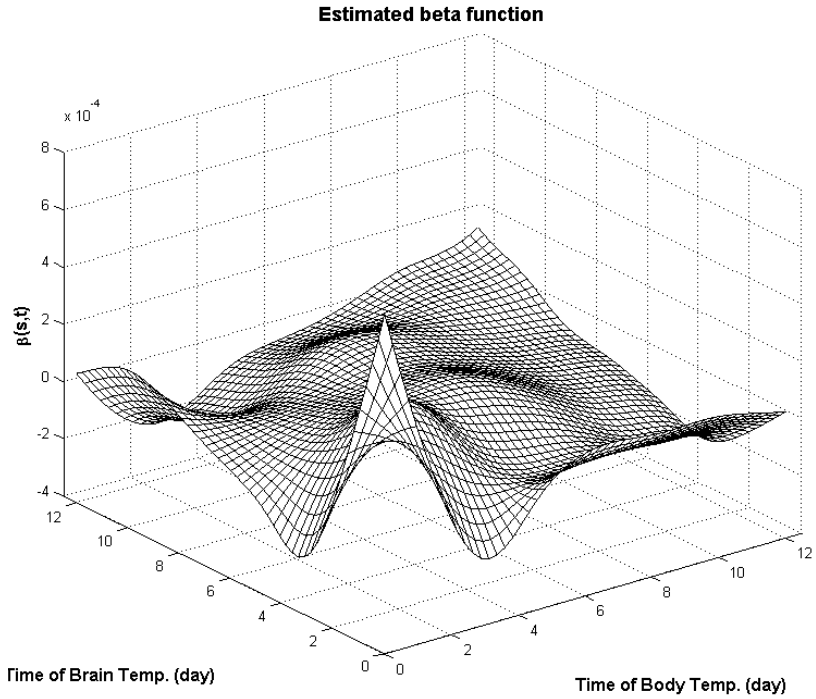

Figure 4: Estimated regression parameter function, Beta, for body temperature as predictor (plotted towards to right) and brain temperature as response (plotted towards to left).

between one's first three day's body temperature and their brain temperature on day 5, a clinician then may decide to pay particular attention to the patient's body temperature in the first three days or even with some possible special medical care. From Figure **4** we can see that in the first two days following severe TBI we found that body temperature is a strong predictor for brain temperature since there Beta values are significantly different from zero.

On any given day, the strength of association between brain temperature and body temperature can be viewed by taking the appropriate cross-section through the Beta surface. These associations are shown in Figure **5**. For example, in the top panel in Figure **5**, the curve for day 0 was plotted by fixing the brain temperature time to be zero and then obtain $\beta(s,0)$. As we can see, there is a strong positive association between body temperature at day 0 and brain temperature at the same day. As these cross-sectional profiles tend to peak on their corresponding days, contemporaneous body temperature is the best predictor of current brain temperature. However, associations beyond day 2 are weak and less consistent.

The negative association between day 0 brain temperature and day 3 body temperature apparent in Figure **5** may be a result of treatment interventions or drug administration which disrupts the relationship between the two body sites and which leads to temperature dissociation. An alternative explanation might lie with the possibility that infection could influence the relationship between brain and body sites, However, this must be a matter for conjecture only and a justification for further hypothesis testing in a future prospective study design. This illustrates that body temperature on one specific day is not a good predictor of brain temperature at other times.

DISCUSSION

Knowledge of human brain temperature remains limited principally due to a lack of reliable non-invasive

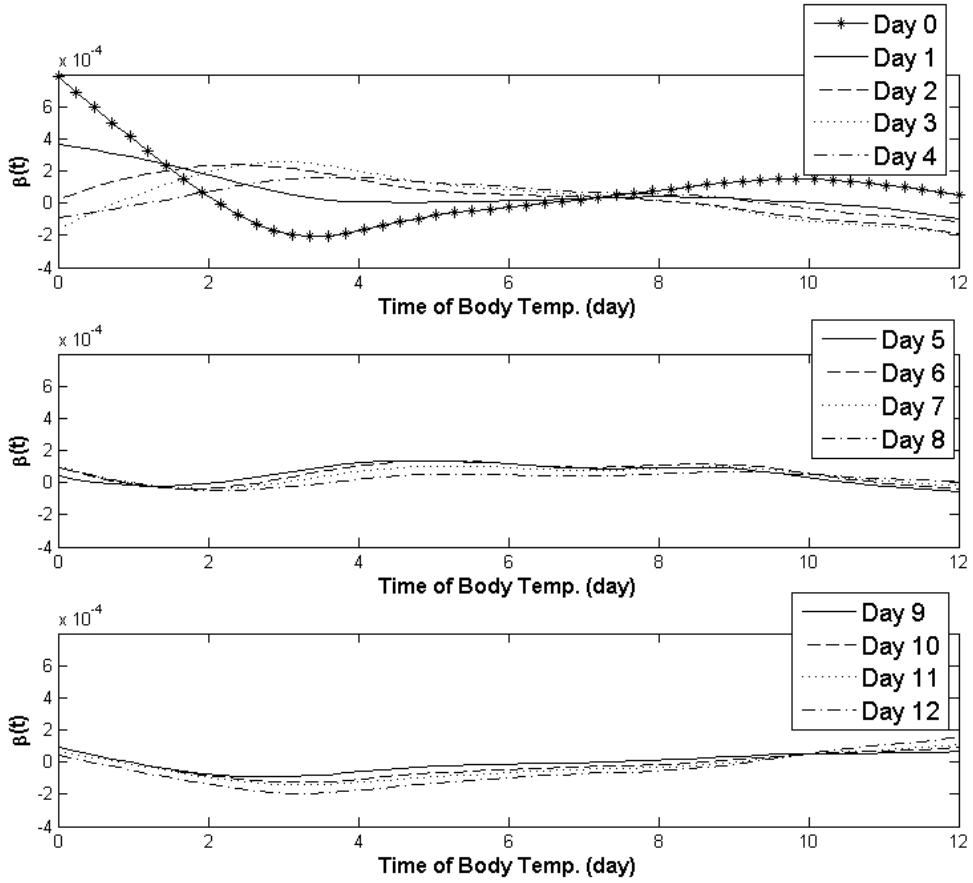

Figure 5: Example of weight function, Beta, for predicting brain temperature at different days. Cross-sectional profiles of the Beta function (see Figure **3**) for fixed days of brain temperature. For example, for day 0 brain temperature, the association with day 0 body temperature is very strong, drops rapidly to a negative association with day 3 and then returns to little association for the remaining time. For day 2 brain temperature the association rises to a peak with day 2 body temperature and tails off gradually thereafter.

measurement technology. That said, one area of investigation where our understanding of cerebral homoeothermy is increasing, is in the sphere of brain trauma [19]. Insertion of sensors directly in to brain tissue once restricted to the laboratory is now justified in man on clinical grounds because current practice guidelines recommend the insertion of sensors for measurement of intracranial pressure (BTF guidelines) in patients with severe brain injury [20]. With the insertion of one sensor, other sensor types can follow, in the form of multi-parameter sensors. Currently it is possible to insert a single probe containing three different microsensors (for example, pressure, temperature and oxygen) and this technology not only augments clinical monitoring but advances our understanding of the impact of temperature change on other physiological variables.

Sensors implanted within brain need to be sited at a depth which is 'shielded' from the ingress of environmental temperature [21]. In adult man, this shielding length is 4mm. In the current study, sensors were implanted to a depth of approximately 3cm within white matter of the right frontal lobe [13]. The question of whether body temperature can serve as a reliable surrogate for brain tissue (or ventricular) temperature has significant clinical relevance. Whilst it has always been attested that tympanic membrane temperature provides the best approximation to brain temperature without the need for surgery [22], we have shown previously, the lack of agreement between brain and tympanum with tympanum over- and under-estimating brain temperature by as much as 3^{o}C in some cases [23]. Such errors are likely due to poor measurement practice leading to measurement error. Of the other conventional measurement sites commonly used in clinical practice [24] rectal temperature is the least invasive and potentially the most useful. The problem is that rectal monitoring is not popular and probes are prone to displacement. However, if the probe can be secured carefully and measurements are reliable, the possibility of evaluating the temporal inter-relationship between brain and body sites can be realized. By studying the temperature dynamics of brain–injured patients we have demonstrated that body temperature performs well as a predictor for brain temperature but during the first two days after injury only. Forecasting of brain temperature from body temperature on different days is not reliable. Due to the dynamics of rapid changes in heat storage (and heat loss) this is an entirely reasonable argument against forecasting subsequent temperature profiles in future mathematical modeling studies.

The question remains, why should a temperature measurement at a site (e.g. rectum) and distant from the target temperature (brain) perform as a reliable surrogate? Studies in non-human primates show that arterial blood carries temperature fluctuations to the brain [25] but during periods of normal cerebral blood flow in the freely moving animal, brain temperature remains constant but at a higher temperature than arterial blood. During experimental vasodilation in monkey, blood flow accelerates and the cooler arterial blood flow through the brain increases removal of cerebral metabolic heat from the (slightly) warmer brain. By removal of heat from the brain, the brain-body temperature gradient narrows. In non-anaesthetized, non-human primates, brain is 0.4^{o}C warmer than blood temperature [25]. Subsequent studies by the group of Hayward and Baker showed that there are species differences in the direction of the temperature gradient between brain and body. For example in 'carotid rete' species (sheep, dog, cat) brain cooling below arterial blood temperature is possible due to the anatomical structure of the rete mirabile [26]. This complex of small parallel arteries course through a venous lake, the cavernous sinus (cooled by air of the nasal cavity) and acts as a counter current heat exchanger such that blood arriving at the circle of Willis (and hence to brain) is at a lower temperature than carotid blood and explains why brain is cooler than carotid artery blood. This is not the case however in man; in the absence of the 'rete mirabile', carotid artery blood is 'close' to blood temperature at the circle of Willis. Knowledge that the temperature of the incoming arterial blood in man is a plausible reference for body core temperature has important clinical utility. That there is no anatomical structure specifically designed as a counter current heat exchanger to lower brain temperature below carotid artery temperature in man, indicates that providing accurate measurement of core tissues can be obtained, deep body tissue (including rectum) has potential as a surrogate for brain temperature. In the current study we have established, in a clinical setting, and by examining time-dependent relationships between brain and body (rectal) temperature that the relationship is strong. However, it is our proposition that the clinical and physiological events which occur during the course of treatment and after the initial acute period is over makes prediction of brain temperature from body temperature reliable only during the first 48 hours (2 days) after injury.

In this study, functional regression methods were used to handle the large size datasets from the

patients, including those where trajectories are sampled at numerous fixed time-points. However, the technique is also appropriate for sparsely sampled data in random designs [16]. Furthermore functional regression can accommodate missing observations. By using a nonparametric approach, functional regression is highly flexible and works under minimal assumptions. No stationarity is required (as by some time series approaches) and the availability of associated graphics software allows visualization and characterization, as in this study, of the nature of the functional relationship between brain and body temperatures trajectories.

Collaborations between clinicians and mathematicians should be encouraged for the future, not least to take advantage of the vast datasets acquired in contemporary health care and which, in the majority of healthcare settings where continuous data is available, are either overlooked or disregarded as too complex to acquire or to analyse. Yet, rich data is available which may, for the future, influence clinical decision making in areas of critical care that had not been contemplated. In this respect we acknowledge other key physiological parameters (intracranial pressure, brain tissue oxygen, cerebral perfusion and blood flow) which are either commonly measured as routine or are measurements 'on the horizon' for future customary practice. We might predict, warrant investigation of time-dependent temporal relationships in an effort to understand and progress our knowledge of recovery and outcome from severe trauma.

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AUTHOR CONTRIBUTION

C. Childs: Devised the study, collected the data and wrote the paper.

K Liu: Undertook statistical analyses and co-wrote the paper.

A Vail: Co-wrote the paper and contributed to clinical and mathematical discussions.

J Pan: contributed to the discussions and to the overview of statistical analyses.

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