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Model of local temperature changes in brain upon functional activation

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Collins, Christopher M., Michael B. Smith, and Robert Turner. Model of local temperature changes in brain upon functional activation. *J Appl Physiol* 97: 2051–2055, 2004. First published August 20, 2004; doi:10.1152/japplphysiol.00626.2004.—Experimental results for changes in brain temperature during functional activation show large variations. It is, therefore, desirable to develop a careful numerical model for such changes. Here, a three-dimensional model of temperature in the human head using the bioheat equation, which includes effects of metabolism, perfusion, and thermal conduction, is employed to examine potential temperature changes due to functional activation in brain. It is found that, depending on location in brain and corresponding baseline temperature relative to blood temperature, temperature may increase or decrease on activation and concomitant increases in perfusion and rate of metabolism. Changes in perfusion are generally seen to have a greater effect on temperature than are changes in metabolism, and hence active brain is predicted to approach blood temperature from its initial temperature. All calculated changes in temperature for reasonable physiological parameters have magnitudes <0.12°C and are well within the range reported in recent experimental studies involving human subjects.

perfusion; metabolism; heat; calculations

IN GENERAL, WHEN A PERSON performs a cognitive or perceptual task, specific regions of the brain increase their activity, resulting in local increases in metabolism and perfusion. In theory, this could result in a change in local brain temperature (T). Previously, a variety of methods have been used in attempts to correlate changes in local brain T with functional activation.

Measurements by thermocouples inserted into the brain of anesthetized cats (17) indicated an increase of ~0.015°C in the lateral geniculate nucleus and visual cortex following visual stimulation. With the use of similar methods, another group (11) measured slight (0.001–0.01°C) T decreases in the lateral geniculate nucleus of anesthetized cats during visual stimulation but a more significant (0.1–0.25°C) T increase in awake animals using the same procedure. They also measured a slight (0.001–0.015°C) increase in T in the inferior colliculus of anesthetized cats following auditory stimulation (11), and slight (0.0005–0.01°C) T increases in the thalamus, ventral posteromedial nucleus, and reticular formation of anesthetized cats during somatic stimulation (12). Using probes near the cortical surface, another group (10) reported transient T increases of ~0.1°C following direct electrical cortical stimulation in anesthetized rats.

In a large number of studies (4, 5, 18–20), the T of the surface of the skull or scalp was measured by using infrared cameras in a variety of species during a number of types of stimulations, and deductions were made about the T of the underlying cerebral cortex. Because the sources of infrared energy that can be detected directly with this method must be in the outermost 100 μm of the exterior surface of the exposed skull or scalp (5), deductions about the T of the underlying cerebral cortex require consideration of thermal conductivity, heat of metabolism, and rate of perfusion in all tissues between the cortex and the air. No careful analysis of these effects is presented in these works. Using these methods in conjunction with visual stimulation in anesthetized rats with the skull exposed, T increases ranging from 0.025 to 1.4°C have been reported (5, 19).

In at least two recent reports (3, 6), infrared cameras were used to detect T changes (ΔT) directly on the surface of the brain after craniotomy and dural opening in conscious human subjects during a number of different functions and stimuli. Ecker et al. (3) reported that, in 4 of 11 subjects, there was a correlation between T on the surface of the speech cortex and verbalization, and in 3 of 11 subjects there was a correlation between T on the surface of the motor cortex and hand motion. In the example case given, there was an increase in T on the surface of the speech cortex of ~0.7°C during verbalization. Gorbach et al. (6) reported that, in cases involving median nerve stimulation, hand movements, finger tapping, and speech productions, reproducible T increases of 0.04–0.08°C were recorded in the appropriate areas.

Using an MRI thermometry technique, one group has reported a mean decrease in T deep in the calcarine fissure of 0.2°C on visual stimulation in conscious human subjects (24), with values ranging as large as 1°C.

Given this large variation in measured results, a numerical study of possible ΔT in the brain during activation for normal physiological parameters is warranted. Here we apply a finite difference implementation of the Pennes bioheat equation (15) to a three-dimensional, multitissue model of the human head and then simulate activation in the calcarine fissure by increasing rates of metabolism and perfusion in this region by appropriate amounts and calculating the resulting effect on the T distribution.

MATERIALS AND METHODS

Creation of head model. A model of the human head was created by first segmenting 120 digital photographic images of axial slices through a male cadaver from the National Library of Medicine's Visible Human Project into 20 materials (18 tissues, air, and metal dental filling) and then transforming these segmented images into a three-dimensional grid of cubic voxels. Segmentation was performed in a largely manual method with reference to textbooks on anatomy

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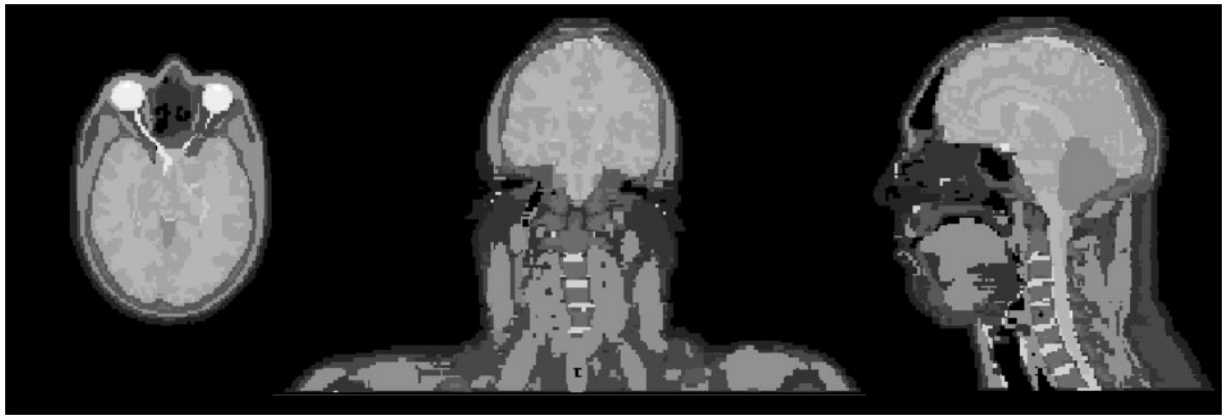

Fig. 1. Three-dimensional geometry of entire head model.

and with advice from two practicing radiologists. The final model grid resolution was (Δ_x, Δ_y, Δ_z) = (2 mm, 2 mm, 2 mm), where Δ_x is in the model's left-right direction, Δ_y is in the model's anterior-posterior direction, and Δ_z is in the model's inferior-superior direction. A few slices through the model are shown in Fig. 1.

T calculation method. T was calculated in the head model with a finite difference implementation of the Pennes bioheat equation (15)

$$\rho c\frac{dT}{dt} = \nabla \cdot (k\nabla T) + [- \rho_{blood} w c_{blood} (T - T_{blood})] + Q_m \quad (1)$$

where ρ is material density, c is heat capacity, t is time, k is thermal conductivity, ρ_{blood} is blood ρ, w is perfusion by blood, c_{blood} is blood c, T_{blood} is blood T, and Q_m is heat of metabolism. Values for ρ, c, k, w, and Q_m for the different tissue types were acquired from the literature (2, 7, 16, 22, 23). The values used in these calculations are given in Table 1, unless otherwise noted. Values for w are given in milliliters of blood through 100 g of tissue each minute. The value of 1,000 ml·100 g^{-1}·min^{-1} is assigned to blood tissue so that the T in blood vessels, most notably the superior sagittal sinus, will remain very close to T_{blood}. Except where otherwise noted, T_{blood} was set to 37°C. This equation was solved at all points in tissue with the condition at the boundary between tissue and air outside the head; T in air was 24°C. The finite difference implementation was achieved by using first-order central difference approximations for all derivatives with respect to position and a first-order forward difference approximation for the derivative with respect to time. With the initial condition of all T values being known (all tissue T values initially equal to that of blood for the calculation of resting equilibrium T and initially equal to resting equilibrium T for calculation of increase in T due to functional activation), there is only one unknown at each location at each point in time, namely the T value at that location at the next point in time. Thus an algebraic equation is solved at all locations at progressive points in time for the T at the next point in time until a new equilibrium is reached where the T no longer changes with time. Validation of our finite difference implementation was performed by comparison with two analytic solutions (1).

Simulation of local brain activation for "normal" physiological parameters. For simplicity, it was assumed that w was independent of T, T_{blood} was a constant 37°C, and ambient T was 23°C. A baseline equilibrium T distribution was first calculated. Then w and Q_m for the gray matter in the calcarine fissure were increased by 50 and 25%, respectively (9), and a second T calculation was performed. When the T distribution reached its new equilibrium, the new T distribution was recorded.

Variation in physiological parameters. To examine what ΔT may be possible for various physiological parameters, this process was repeated for T_{blood} from 36 to 40°C, for baseline w of gray matter from 10 to 100 ml·100 g^{-1}·min^{-1}, and for percent changes in w and Q_m in gray matter on activation from 20 to 100% and from 10 to 70%, respectively.

RESULTS

Model geometry, baseline T (T_{base}) distribution, and ΔT on activation of gray matter in the calcarine fissure for normal physiological parameters are given in Fig. 2. In central brain

Table 1. *Material properties and physiological parameters used in calculations*

Material/Tissue	w, ml·100 g^{-1}·min^{-1}	ρ, kg/m^3	c, J·kg^{-1}·°C^{-1}	k, W·m^{-1}·°C^{-1}	Q_m, W/m^3
Air	0	1.3	1,006	0.026	0
Blood	1,000	1,057	3,600	0.51	0
Cancellous bone	3	1,080	2,110	0.65	26.1
Cerebellum	45.2	1,035.5	3,640	0.534	11,600
Cerebrospinal fluid	0	1,007	3,800	0.50	0
Cortical bone	1.35	1,850	1,300	0.65	26.1
Esophagus	40	1,126	3,720	0.527	697
Eye: sclera/cornea	0	1,076	3,000	0.40	0
Eye: vitrous humor	0	1,009	4,200	0.594	0
Fat	2.8	916	2,300	0.25	302
Gray matter	67.1	1,035.5	3,680	0.565	15,575
Tendon, other	3.8	1,151	3,500	0.4975	0
Muscle	3.8	1,041	3,720	0.4975	697
Skin	12	1,100	3,150	0.342	1,100
White matter	23.7	1,027.4	3,600	0.503	5,192

w, Perfusion by blood; ρ, material density; c, heat capacity; k, thermal conductivity; Q_m, heat of metabolism.

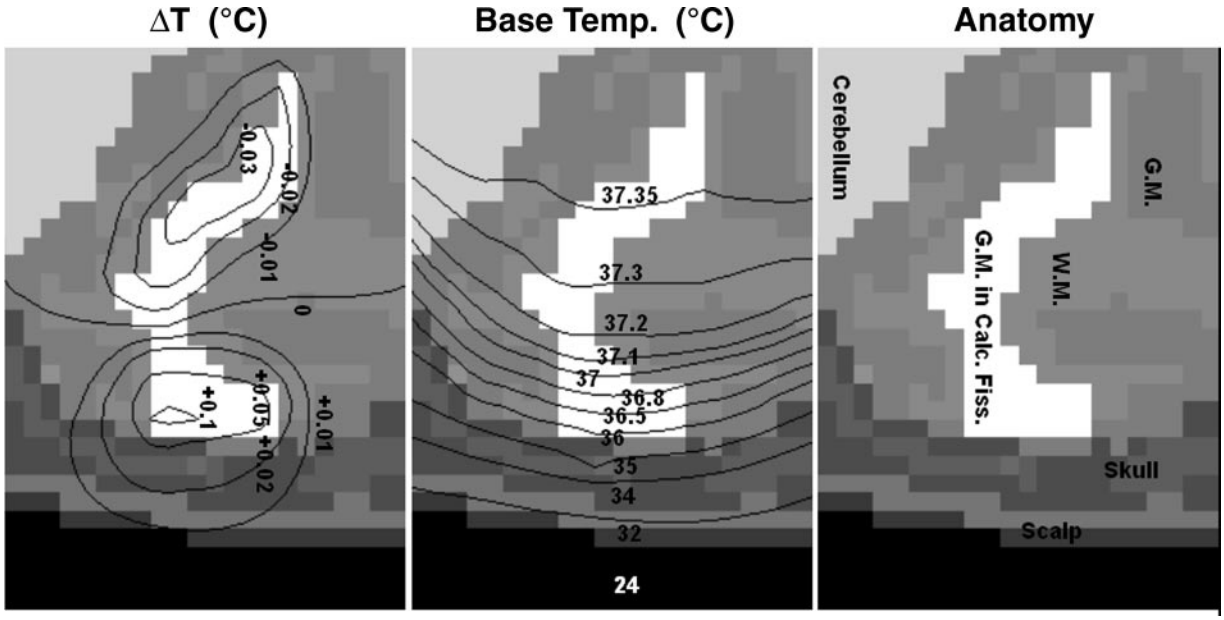

Fig. 2. Model geometry (*right*), baseline temperature distribution (*middle*), and change in temperature on activation (ΔT; *left*) of gray matter (GM) in calcarine fissure for normal physiological parameters. Slice shown is on sagittal section through calcarine fissure of complete three-dimensional head model. Blood temperature is 37°C. Model resolution is 2 mm. WM, white matter.

regions, T_{base} is typically slightly greater than T_{blood}, and in more peripheral regions T_{base} is typically slightly less than T_{blood} (Fig. 1). This baseline distribution is quite consistent with other calculations and is not seen to change greatly with more extensive modeling of vasculature in the brain (14, 23). A baseline distribution with a similar distribution and range (a few tenths of 1°C) was also seen in experimental measurements in the cat brain (11, 12). On activation, the effect of the increase in perfusion is to slightly cool the brain in more central regions of activation (where $T_{base} > T_{blood}$) and, in concert with the increased rate of metabolism, slightly warm the brain in more peripheral regions of activation (where $T_{base} < T_{blood}$). In these results, there are no regions where ΔT exceeds 0.12°C.

Variation in physiological parameters. When T_{blood} is varied from 35 to 40°C, there is little change in ΔT, largely because both initial and final T closely follow variations in T_{blood}.

When resting gray matter w is varied from 40 to 90 ml·100 g^{-1}·min^{-1}, the minimum ΔT varies from −0.035°C at 40 ml·100 g^{-1}·min^{-1} to −0.034°C at 90 ml·100 g^{-1}·min^{-1} with a nadir of −0.037°C at 60 ml·100 g^{-1}·min^{-1}, and the maximum ΔT decreases monotonically from 0.114°C at 40 ml·100 g^{-1}·min^{-1} to 0.106°C at 90 ml·100 g^{-1}·min^{-1}.

Minimum and maximum ΔT for variation in percent changes in perfusion and rate of metabolism in gray matter on activation are shown in Fig. 3, with an asterisk marking the results for approximate normal physiological values. In general, ΔT is

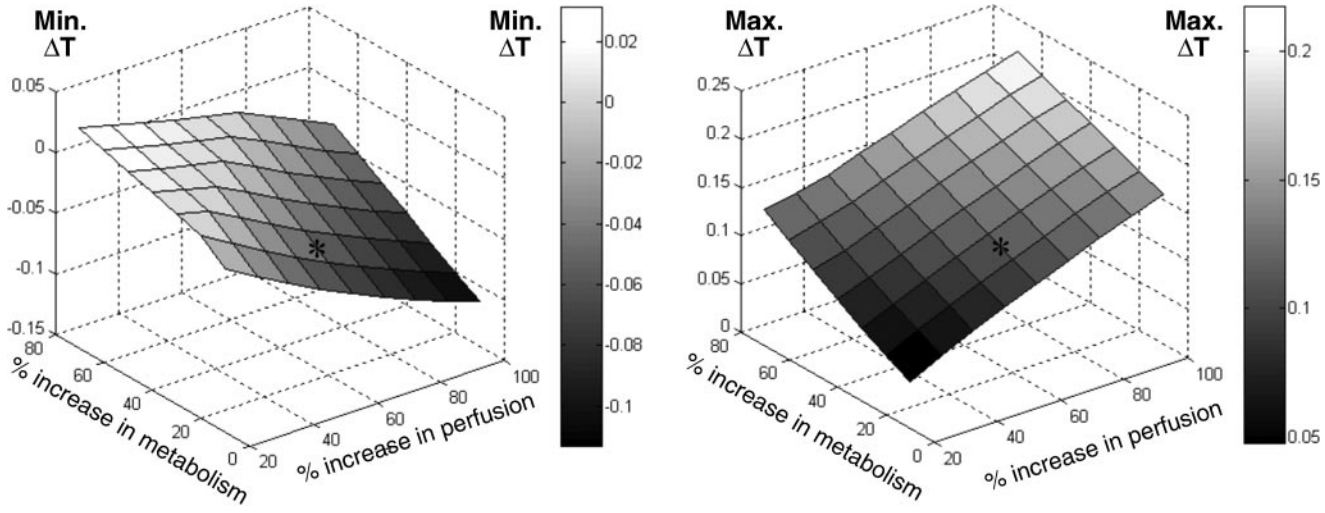

Fig. 3. Minimum (*left*) and maximum (*right*) ΔT as functions of both increase in rate of perfusion and increase in rate of metabolic heat generation. Asterisks mark ΔT for physiological values believed typical for maximal activation (8) for normal physiological parameters and those used for results in Fig 1.

seen to increase for increasing change in Q_m. Minimum ΔT (occurring in deeper locations where $T_{base} > T_{blood}$) decreases with increasing change in w, whereas maximum ΔT (occurring in peripheral regions where $T_{base} < T_{blood}$) increases with increasing change in w. Over the entire range of "activation" changes in w and Q_m, minimum and maximum ΔT stay within $\sim$0.1°C of their values for "normal" physiological parameters.

DISCUSSION

There is a large disparity in the literature regarding experimentally measured ΔT in brain following some sort of stimulus. Possible factors affecting experimental measurements include method of measurement, type of stimulus, choice of anesthetic, species, and even age of the subject. For example, a brain T decrease of >0.5°C was reported in 5-day-old rat pups during physical stimulation designed to simulate contact with the mother, but not in 10-, 15-, or 20-day-old rat pups (21). Conversely, a brain T increase of 0.05–0.1°C was recorded at several locations in the brains of adult cats during a period of interaction with and petting by a person (25). Both of these stimuli may evoke complex emotional responses, and even whole body physiological responses. For example, in the case of the 5-day-old rat pups, physical stimulation resulted in an increase in respiration and decrease in whole body T. Use of anesthetic may affect brain function and w. Use of invasive probes may affect local blood flow, and exposure of the cerebral cortex to ambient air will likely affect the T_{base} distribution.

With the use of a mathematical model, it is possible to begin to sort out the possible effects of the many different variables on T in a well-controlled manner. This work presents a first attempt to model changes in brain T during functional activation in a three-dimensional anatomically accurate numerical model. Although our numerical method compares very well to analytic solutions of simple systems (1), the model is limited in that only the largest details of vasculature, veins and arteries >5 mm in diameter, are included, and baseline T_{blood} and most physiological properties are assumed to be independent of time and position within a given tissue type. Also, it is assumed that physiological values change only in one region of brain in a very specific manner, when, in reality, the brain is a very dynamic organ, performing many tasks simultaneously. Although very large baseline spatial T gradients have been observed to be associated with the vasculature when the cortex is exposed (6), models including increasing degrees of vascularity show little difference in T_{base} distribution for intact anatomy (23). Brain T is likely to be much more homogeneous when insulated by the intact skull and scalp.

The effects of perspiration and radiation are not considered in this model. Although perspiration and radiation are indeed known to be important in overall thermoregulation and in heat transfer at the surface of the body, in this particular case it is unlikely that either sweating or radiation will have much of a direct effect on local ΔT in the brain cortex, centimeters away from the surface of the body. Here we are assuming the subject has a core body T of 37°C and is in a room of 24°C T. In this situation, it is not expected that perspiration will be significant (13). Also, the portion of the skin nearest the calcarine fissure is typically covered with hair, reducing and complicating the effects of radiation in this region (8). Modeling the effects of perspiration and radiation would also require many more assumptions regarding quantities like humidity of ambient air and amount of sunlight incident on the skin. Ultimately, in this case, the relevant question becomes whether the skin T arrived at by the model is reasonable. A skin T a little below 32°C, as found in our model, is very near the mean skin T for a human subject at 24°C but perhaps as much as 1°C below forehead T in the same case (8). If the surface of the skin were somehow increased by 1°C or so, this might cause the contours for T_{base} near the surface of the body in Fig. 2 to spread out and shift slightly to the right and cause the contours for ΔT near the surface of the body to move slightly to the left and closer together but should not affect any of the main conclusions of this work.

Results from this study predict ΔT ranging from about −0.03°C to about +0.1°C for "normal" physiological parameters. This is well within the ranges published in the recent literature for human studies: from approximately −0.2°C (24) to approximately +0.7°C (3). It is possible that, in experiments in which the cortex is exposed, the T_{base} of the cortex would be significantly less than would be expected normally, so the effect of perfusion may indeed raise the T by several tenths of a degree (3), although one such study reported changes no greater than 0.08°C using similar methods (6).

This work also illustrates that, due to the effects of increased perfusion and the T distribution of the brain at rest, it is possible to have a T increase with activation in peripheral regions of the human brain (3, 6) and a T decrease with activation in deeper regions (24).

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