BRAIN TEMPERATURE MEASUREMNT BY MAGNETIC RESONANCE SPECTROSCOPY THERMOMETRY USING REGRESSION ANALYSIS

A.N. Mumuni[1], M.M. Salifu[2], M.N. Abubakari[1]

[1] Department of Medical Imaging, University for Development Studies, Tamale, Ghana
[2] Department of Medical Physics, University of Ghana, Accra, Ghana

***Abstract*— Information about core brain temperature is relevant for monitoring the physiological state of the body under both healthy and pathological conditions. Apart from standard clinical methods, various techniques have been proposed specifically for brain temperature measurement using magnetic resonance spectroscopy (MRS) thermometry. The commonest method is the calibration of the water frequency shift relative to the N-acetyl aspartate metabolite peak. This technique is based on temperature-dependent displacement of the water peak from its normal frequency position. Existing MRS thermometry methods are often associated with challenges of direct clinical utility, particularly where additional information about brain metabolism is required. This study deduced standard calibration equations using regression analysis for brain MRS thermometry. Clinically measured brain temperature (T_{brain}) using a temperature gun was used as the dependent variable and the water frequency shift from the NAA, creatine and choline peaks were each used as independent variables in separate regression analyses to yield equations of the form: Brain temperature (T_{brain}) = $k_1(\Delta H_2O - \delta_{met}) + k_2$, where k_1 is the gradient of the regression fit, k_2 is the intercept of the regression fit on the T_{brain} axis, ΔH_2O is the new water frequency after temperature-dependent shift, and δ_{met} is the normal frequency of the particular reference peak on the ppm axis (2.01, 3.03, and 3.20 ppm for NAA, creatine, and choline, respectively). The equations were validated in a separate group of healthy subjects and were found to provide accurate temperature estimates, with reproducibility better than 2.0 %. Future studies are required to assess the utility of the equations in study participants with a wide range of physiological characteristics.**

Keywords— **brain, magnetic resonance spectroscopy, temperature, thermometry, regression**

I. INTRODUCTION

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a nuclear magnetic resonance (NMR) technique that is capable of measuring brain metabolism noninvasively and *in vivo*. Normal brain function or pathology can be inferred from the biochemical profile obtained from a typical ^{1}H-MRS data [1,2]. In addition to the biochemical information, subtle changes in core brain temperature associated with physiological activities in the body can also be probed by ^{1}H-MRS [3]. Temperature variation causes a slight displacement of the water peak from its normal frequency position in the ^{1}H-MR spectrum. The N-acetyl aspartate (NAA) peak, unaffected by the temperature variation, is mostly used as the reference peak relative to which the water peak displacement is measured, and this frequency difference can be converted to temperature estimate [4,5]. This procedure is often called MRS thermometry.

The balance between heat produced by cerebral metabolism and heat dissipated by cerebral blood flow determines the temperature of the brain in healthy individuals at rest [6-8]. The need for early biomarkers of brain swelling is crucial because decompressive surgery performed before clinical deterioration can improve treatment outcomes [9]. Pathologies are associated with subtle biochemical changes in the body which often do not show in anatomical imaging, but can be probed by ^{1}H-MRS. In pathologies where core body temperature is elevated, the MRS data may require some adjustments or corrections to be optimized before it can be used to estimate absolute metabolite concentrations. The ^{1}H-MRS method allows for a reasonably precise measurement of brain temperature noninvasively and *in vivo* [10] by comparing the chemical changes of water protons to an abundant internal reference, such as NAA [4,5,11], creatine [12], or choline [3]. Indirect brain temperature measurements, such as MRS thermometry, often require some sort of calibration techniques to estimate temperature [13]. This therefore makes them unsuitable for routine clinical application due to associated patient compliance issues and inaccuracies in the estimates.

This paper provides a procedure for the establishment of a standard procedure to deduce calibration equations that can be used for brain temperature estimation using MRS thermometry. The technique is applicable to clinical ^{1}H-MRS acquisition, as long as the water peak frequency can be obtained from the acquired data.

II. MATERIALS AND METHODS

A. STUDY PARTICIPANTS

Following the approval of the study protocol by the University of Ghana Ethics Committee for Basic and Applied Sciences (ECBAS) and the University of Ghana Medical Centre (UGMC) Institutional Review Board, seven (7) healthy volunteers (5 males/2 females, aged 22-43 years) participated in the study. No study participant had any

magnetic resonance imaging (MRI) contraindication or neurological condition.

B. MRI/MRS ACQUISITION

Data was acquired on a 1.5 T Philips Ingenia MRI/MRS System, equipped with a quadrature radiofrequency head coil.

Prior to going into the MRI bore, brain temperature of each study participant was taken at their forehead using an infrared (IR) temperature gun, and recorded as T_{IR}.

Structural MRI of the brain was acquired using the T_1-weighted 3-dimensional turbo field echo sequence. Using the acquired MRI, voxel sizes were varied to fit the head size of each participant, typically ensuring a longer anterior-posterior dimension and positioning above the corpus callosum (Figure 1). Outer volume shimming for B_0 inhomogeneity was performed using both linear and second-order shims. ^{1}H-MRS acquisition was performed using the standard Point RESolved Spectroscopy (PRESS) pulse sequence (TE/TR = 144 ms/2000 ms), which yielded the dominant spectral peaks of NAA, creatine, choline and water (not shown in Figure 2).

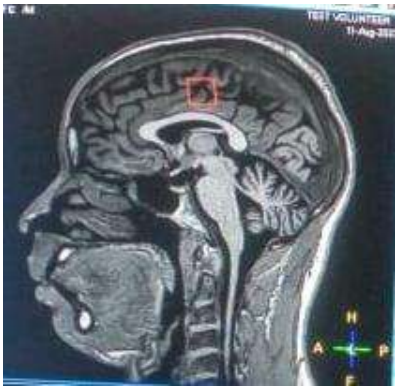

Figure 1: Voxel position in the brain MRI of a participant

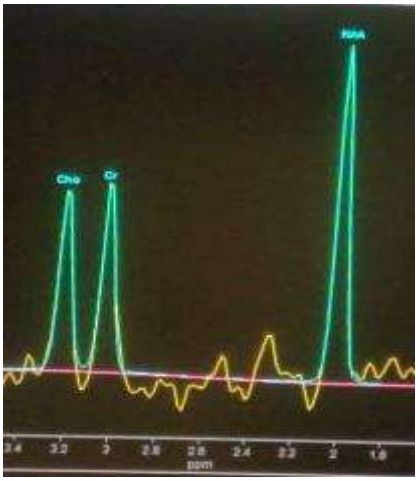

Figure 2: Spectral peaks of NAA, creatine, and choline at 2.01 ppm, 3.03 ppm and 3.20 ppm respectively

C. TEMPERATURE EQUATION

The raw spectral data were Fourier transformed to the frequency domain, and corrected for baseline and phase distortions in the jMRUI software (version 6.0). The NAA, creatine, and choline resonant frequencies visually were inspected to ensure that they were at their expected positions. Each ^{1}H-MRS data was zoomed on the water peak (Figure 3) to observe the frequency variations in its position which were then recorded from the jMRUI analysis. Using each one of the spectral peak frequencies of NAA, creatine and choline (denoted by δ_{met}) as the reference, the frequency shift of the water peak from each reference peak was calculated as ($\Delta H_2O - \delta_{met}$).

A regression fit to the scatter plot of T_{IR} versus ($\Delta H_2O - \delta_{met}$) yielded an equation of the form:

$$T_{brain} = T_{IR} = k_1(\Delta H_2O - \delta_{met}) + k_2 \quad (1)$$

where k_1 is the gradient of the regression fit, k_2 is the intercept of the regression fit on the T_{brain} or T_{IR} axis, ΔH_2O is the new water frequency after temperature-dependent shift on the ppm axis of the frequency-domain spectra, and δ_{met} is the normal frequency of the particular reference peak on the ppm axis.

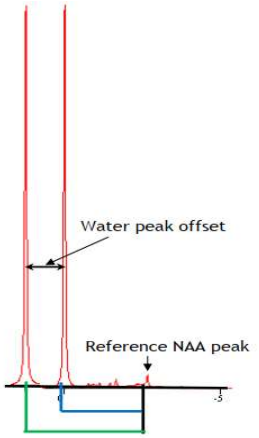

Figure 3: Temperature-dependent water frequency shift from its normal position, away from the reference NAA metabolite spectral peak

D. STATISTICAL ANALYSIS

The clibration equations were validated in a separate group of healthy volunteers whose temperature measurements were previously taken using the infrared temperature gun. Reproducibility of the measured MRS thermometric brain temperature using each equation was assessed by the coefficient of variation (CoV) for repeated measures, calculated as:

$$CoV = (\text{standard deviation/mean}) \times 100\ \% \quad (2)$$

The thermometer and MRS thermometry tempearature measurements were compared for differences using the paired t-test, assuming normality of the data.

III. RESULTS

Tables 1-3 show the infrared temperature gun measurements (T_{IR}) and their corresponding calculated frequency displacements (ΔH_2O-δ_{met}) of the water peak (ΔH_2O) from the respective reference metabolite spectral peaks (δ_{met}). T_{IR} was used as the dependent variable while (ΔH_2O-δ_{met}) was used as the independent variable in the regression analysis.

Table 1 Water frequency shift from the NAA reference peak

T_{IR} (°C)	ΔH_2O (ppm)	δ_{NAA} (ppm)	ΔH_2O-δ_{NAA} (ppm)
36.2	4.65	2.01	2.64
35.7	4.32	2.01	2.31
36.0	4.65	2.01	2.64
36.1	4.63	2.01	2.62
36.2	4.66	2.01	2.65
36.0	4.58	2.01	2.57
35.8	4.40	2.01	2.39

Table 2 Water frequency shift from the creatine reference peak

T_{IR} (°C)	ΔH_2O (ppm)	δ_{Cre} (ppm)	$\Delta H_2O - \delta_{Cre}$ (ppm)
36.2	4.65	3.03	1.62
35.7	4.32	3.03	1.29
36.0	4.65	3.03	1.62
36.1	4.63	3.03	1.60
36.2	4.66	3.03	1.63
36.0	4.55	3.03	1.52
35.8	4.40	3.03	1.37

Table 3 Water frequency shift from the choline reference peak

T_{IR} (°C)	ΔH_2O (ppm)	δ_{Cho} (ppm)	$\Delta H_2O - \delta_{Cho}$ (ppm)
36.2	4.65	3.2	1.45
35.7	4.32	3.2	1.12
36.0	4.65	3.2	1.45
36.1	4.63	3.2	1.43
36.2	4.66	3.2	1.46
36.0	4.55	3.2	1.35
35.8	4.40	3.2	1.20

Table 4 shows the deduced regression equations calibrated for *in vivo* MRS thermometry.

Table 4 Calibrated regression equations for brain MRS thermometry

Reference peak	Regression equation	R^2
NAA	$T_{brain} = 1.3280(\Delta H_2O\text{-}2.01) + 32.626$	0.8909
Cr	$T_{brain} = 1.3275(\Delta H_2O\text{-}3.03) + 33.987$	0.8843
Cho	$T_{brain} = 1.3275(\Delta H_2O\text{-}3.20) + 34.213$	0.8843

The equations were validated using single-voxel ^{1}H-MRS data previously acquired from the frontal brain region of six healthy volunteers. This data was not included in the regression analysis, but was strictly used for the validation of the calibration equations. The averages (± standard errors) of the estimated brain temperatures using the three reference metabolite peaks are shown in Figure 4.

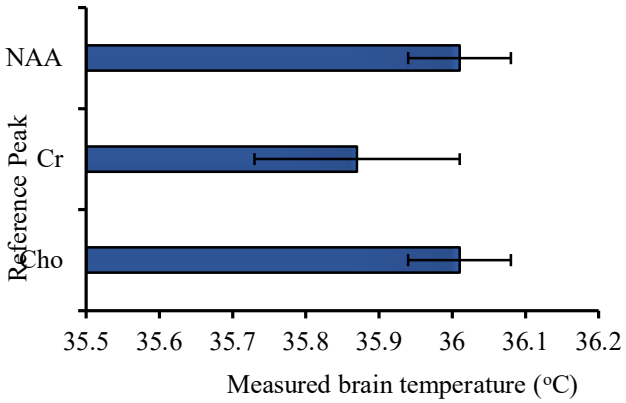

Fig 4 Average brain temperature estimates from MRS thermometry using the derived calibration equations

IV. DISCUSSION

The observed water frequency shifts have been reported to be independent of magnetic susceptibility [14,15]. Even though the NAA peak has been the most preferred reference choice due to its prominence in the MR spectrum and general utility in quantitative ^{1}H-MRS studies, the methods of calibration presented here could be applicable to the creatine and choline peaks as well. The deduced temperature equations are valid for temperature prediction interval of between 35.5 °C and 37.5 °C. Therefore, future *in vivo* brain MRS thermometry studies could directly substitute the measured water frequency shift value into any of the respective calibration regression equations (Table 4) to estimate brain temperature with over 80% accuracy.

The calibration equations were validated using previously acquired clinical ^{1}H-MRS data with accompanying brain temperature measurements. There were no significant differences between the ^{1}H-MRS thermometric estimates from each of the derived equations (Table 4) and the previous clinical thermometer temperature measurements by paired t-test ($p > 0.05$). It was noted that the NAA and choline derived equations yielded slightly higher brain temperature values than the creatine derived equation (Figure 4). The reproducibility of the measurements across the validation group, as measured by the CoV, was better than 2.0 % for all the reference peaks.

MRS thermometry studies generally use the NAA peak as a reference, and have used phantoms [16], pH controlled aqueous solutions [3] or MR spectroscopy imaging methods [12] in brain temperature measurements. These methods are largely challenging for direct clinical applications due to the multiple steps and assumptions involved in the brain temperature measurement process. One study [3] used all the three reference peaks as used in this study, and then estimated brain temperature from the average of the measured temperatures from the three reference peak equations. Others have also implemented similar brain temperature

measurement techniques with the NAA reference peak in studies of brain activation during visual stimulation [4,11].

Our proposed method is both straightforward and clinically applicable without patient compliance issues, and yet provides accurate brain temperature estimates as observed in our validation estimates.

Our study and those reported in the literature [3-5,11,12,16] have been consistent in the observation of a linear relationship between the water frequency shift and brain temperature. According to Table 4, for every frequency shift in the water peak away from any of the reference peaks (in ppm), the measured brain temperature will show an increase of about 1.33 ^{o}C. In addition, in the absence of a temperature-associated frequency shift in the water peak, the equations predict a minimum brain temperature within the range of about 33-34 ^{o}C (Table 4). Therefore, our finding of a positive association between the water peak frequency shift and measured temperature is consistent with the findings reported previously. The range of temperatures (35.5-37.5 ^{o}C) used to derive the calibration equations are well within the normal physiological range of human temperature.

It is expected that in pathologies associated with elevated core body temperature, the water peak should drift significantly from its expected frequency position than the observed shifts reported here. This should then scale well with the expected temperature rise in the study subjects. However, such a group of subjects were not included in this study to verify this. Further validation studies of the calibration equations under different study participant conditions (both normal and pathological) are therefore needed to assess their accuracy, reproducibility and wider clinical applicability.

The accuracy of the regression fits and predictions can be enhanced ($R^2 > 0.89$) by a bigger sample size of study participants than used in the current study. The procedure for the establishment and validation of the regression equations should however be reproducible among different studies.

V. CONCLUSIONS

^{1}H-MRS thermometry technique tailored for clinical implementation to measure both brain metabolism and temperature is presented in this paper. Temperature gun measured brain temperature was used to calibrate cerebral water temperature-dependent frequency shift into a temperature measurement through regression analysis. The deduced models were validated and have been found to be accurate for brain temperature measurement within the normal human brain physiological temperature range.

ACKNOWLEDGMENTS

We wish to acknowledge Mr. George Nunoo of the University of Ghana Medical Centre, Accra, Ghana, for his assistance with the MRS data collection. The dedication of all the study participants is very much appreciated.

REFERENCES

1. Mumuni AN, Krishnadas R, Cavanagh J (2023). Peripheral inflammation is associated with alterations in brain biochemistry and mood: evidence from in vivo proton magnetic resonance spectroscopy study. Pure and Applied Chemistry 95(3): 289-300.
2. Hennig J, Speck O, Deuschl G, Feifel E (1994). Detection of brain activation using oxygenation sensitive functional spectroscopy. Magnetic resonance in medicine 31(1): 85-90.
3. Covaciu L, Rubertsson S, Ortiz-Nieto F, Ahlström H, Weis J (2010). Human brain MR spectroscopy thermometry using metabolite aqueous-solution calibrations. Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine 31(4): 807-814.
4. Rango M, Bonifati C, Bresolin N (2015). Post-activation brain warming: a 1-H MRS thermometry study. PLoS One 10(5): e0127314.
5. Cady EB, D'Souza PC, Penrice J, Lorek A (1995). The estimation of local brain temperature by in vivo 1H magnetic resonance spectroscopy. Magnetic resonance in medicine 33(6): 862-867.
6. Ishigaki D, Ogasawara K, Yoshioka Y et al. (2009). Brain temperature measured using proton MR spectroscopy detects cerebral hemodynamic impairment in patients with unilateral chronic major cerebral artery steno-occlusive disease: comparison with positron emission tomography. Stroke 40(9): 3012-3016.
7. Nybo L, Secher NH, Nielsen B (2002). Inadequate heat release from the human brain during prolonged exercise with hyperthermia. The Journal of physiology 545(2): 697-704.
8. Sukstanskii AL, Yablonskiy DA (2006). Theoretical model of temperature regulation in the brain during changes in functional activity. Proceedings of the National Academy of Sciences 103(32): 12144-12149.
9. Schwab S, Steiner T, Aschoff A, Schwarz S, Steiner HH, Jansen O, Hacke W (1998). Early hemicraniectomy in patients with complete middle cerebral artery infarction. Stroke 29(9): 1888-1893.
10. Vescovo E, Levick A, Childs C, Machin G, Zhao S, Williams SR (2013). High-precision calibration of MRS thermometry using validated temperature standards: effects of ionic strength and protein content on the calibration. NMR in Biomedicine 26(2): 213-223.
11. Katz-Brull R, Alsop DC, Marquis RP, Lenkinski RE (2006). Limits on activation-induced temperature and metabolic changes in the human primary visual cortex. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine 56(2): 348-355.
12. Sharma A A, Nenert R, Mueller C, Maudsley AA, Younger JW, Szaflarski JP (2020). Repeatability and reproducibility of in-vivo brain temperature measurements. Frontiers in human neuroscience 14: 598435.
13. Verius M, Frank F, Gizewski E, Broessner G (2019). Magnetic resonance spectroscopy thermometry at 3 tesla: importance of calibration measurements. Therapeutic Hypothermia and Temperature Management 9(2): 146-155.
14. Hashimoto T, Tayaina M, Miyazaki M et al. (1995). Developmental brain changes investigated with proton magnetic resonance spectroscopy. *Developmental Medicine & Child Neurology 37*(5): 398-405.

15. Poorter JD (1995). Noninvasive MRI thermometry with the proton resonance frequency method: study of susceptibility effects. *Magnetic resonance in medicine 34*(3): 359-367.
16. Corbett RJ, Laptook AR, Tollefsbol G, Kim B (1995). Validation of a noninvasive method to measure brain temperature in vivo using 1H NMR spectroscopy. *Journal of neurochemistry 64*(3): 1224-1230.

Contacts of the corresponding author:

Author: Abdul Nashirudeen Mumuni
Institute: Medical Imaging, SAHS-UDS
Street: Dungu-Tamale Campus
City: Tamale
Country: Ghana
Email: mnashiru@uds.edu.gh