Precision and Robustness of Deep Brain Temperature Estimation using Localised Proton Magnetic Resonance Spectroscopy in Normothermic and Hypothermic Newborn Infants

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Background: A Cochrane review **[1]** concluded that therapeutic cerebral hypothermia is an effective and safe treatment for perinatal asphyxial encephalopathy **[2]** with a number needed to treat of 8. Precise knowledge of regional brain temperature is needed in order to optimise therapeutic hypothermia. Proton magnetic resonance spectroscopy thermometry (MRSt) is non-invasive and successfully estimates regional brain temperature in human adults and neonates using the temperature dependence of the water chemical shift **[3,4]**. Reliable absolute temperature measurement depends on good calibration data and robust clinical spectrum acquisition. Detailed calibrations in adult rat brains at 11.4 Tesla, using the major singlet resonances of N-acetyl-aspartate (Naa), choline (Cho) and creatine (Cr) as reference metabolite peaks, have been published by another group **[5]**. Our clinical MRSt implementation uses serial acquisition of subspectra which allows both removal of motion-corrupted data and frequency correction of the remaining subspectra to remove effects of static magnetic field decay and narrow the reference peaks: subspectra are then summed to give the spectrum used to estimate brain temperature.

Aims: (a). To assess the consistency of neonatal brain-temperature estimates at 1.5 Tesla derived using high-field rat-brain calibrations using Cho, Cr and Naa as reference metabolites **[5]** and (b). To assess the advantage of correcting subspectra for static magnetic field decay before summation.

Methods: Forty four neonates had thalamic MRSt to measure deep brain temperature (T_{DB}): 7 had rectal temperature (T_{rec}) measured during MRSt and 37 immediately afterwards. Eight infants underwent therapeutic hypothermia of which 7 were cooled during MRSt. Spectra were acquired on a Siemens 1.5 Tesla Avanto scanner using point-resolved spectroscopy (PRESS) without water-suppression. Acquisition conditions were 1.5x1.5x1.5 cm^3 cubic voxel centred on the left thalamus, recovery time 1370 ms, echo time 288 ms, 2048 complex datapoints. Forty nine subspectra, each with 8 summed transients, were acquired for each examination. The water frequency in each subspectrum was measured by fitting a Lorentzian function using Matlab. The subspectra were then summed with and without correction for magnetic field decay. Summed subspectra were analysed using AMARES **[6]** (jMRUI software **[7]**). The water chemical shift was determined by fitting a single Lorentzian and then the water signal was removed using HLSVD **[8]** (jMRUI software **[7]**): the Naa, Cho, and Cr chemical shifts were also determined using a single Lorentzian for each. Three separate T_{DB}s were estimated from the chemical-shift differences between water and Naa, Cho, and Cr **[5]**.The mean peak linewidths and differences between T_{DB} estimated using Naa, Cho and Cr separately with and without correction for magnetic field decay were tested using paired t-tests. T_{DB} was plotted against T_{rec} and linearly regressed. Correlation between T_{DB} and T_{rec} was tested using the Pearson product moment.

Results: Values are mean (SD). The T_{DB} derived using Naa, Cho, and Cr separately are plotted against T_{rec} in the figure. With the T_{DB} derived using Naa, Cho, and Cr grouped together there was a strong linear correlation with T_{rec} (slope 0.88; $P < 0.0001$, slope not significantly different from 1). The magnetic field decay correction significantly reduced both peak linewidths (Table 1) and differences between the T_{DB} measured using Naa, Cho, and Cr (Table 2). Mean T_{rec} - T_{DB} was -1.0 (0.6)°C.

Discussion: The 11.4-Tesla rat-brain calibrations, acquired with TE 75 ms, yielded Naa, Cho, and Cr neonatal-brain T_{DB} estimations at 1.5 Tesla, collected with TE 288 ms. A mean T_{DB} can be derived from the separate Naa, Cho, and Cr estimates: this should increase precision providing that the 3 separate calibrations are consistent with each other - at TE 75 ms, multiplets adjacent to Naa, Cho, or Cr will be more dominant than at TE 288 ms possibly biasing the apparent reference chemical shifts. T_{DB} measurements were consistent within ~0.4°C. . Splitting data acquisition into subspectra improves MRSt by allowing removal of motion corrupted subspectra and correction for magnetic field decay. T_{rec} has been previously assumed to be a good surrogate for neonatal T_{DB} **[9]**. It is not possible to deduce whether MRSt is overestimating T_{DB} or whether the observed excess compared to T_{rec} is real. This T_{DB} excess is present whichever of Naa, Cho, or Cr is used as reference peak suggesting the water chemical shift may be a source of systematic error. Sources of water chemical-shift perturbation, and interspecies and developmental effects must be carefully considered when translating experimental calibrations to the clinic.

References

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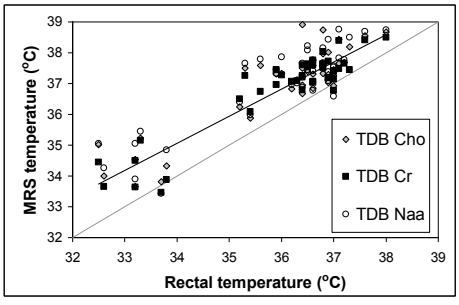

Figure: Correlation between T_{DB} & T_{rec}

	Linewidth (Hz) No Correction	Linewidth (Hz) Frequency Corrected	P
Water	4.2 (0.8)	3.7 (0.8)	< 0.0001
Naa	3.8 (0.8)	3.3 (0.9)	< 0.0001
Cho	3.3 (0.8)	2.7 (0.8)	< 0.0001
Cr	3.4 (0.8)	2.9 (0.6)	< 0.0001

Table 1: Peak linewidths with and without frequency correction

	ΔT (°C) No Correction	ΔT (°C) Frequency Corrected	P
Cho - Naa	0.24 (0.18)	0.22 (0.17)	0.18
Cr – Naa	0.46 (0.40)	0.37 (0.38)	< 0.002
Cho - Cr	0.29 (0.24)	0.24 (0.26)	< 0.01

Table 2: Differences between Temperature estimations using Naa, Cho and Cr with and without frequency correction