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Effects of tissue susceptibility on brain temperature mapping

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ABSTRACT

A method for mapping of temperature over a large volume of the brain using volumetric proton MR spectroscopic imaging has been implemented and applied to 150 normal subjects. Magnetic susceptibility-induced frequency shifts in gray- and white-matter regions were measured and included as a correction in the temperature mapping calculation. Additional sources of magnetic susceptibility variations of the individual metabolite resonance frequencies were also observed that reflect the cellular-level organization of the brain metabolites, with the most notable differences being attributed to changes of the N-Acetylaspartate resonance frequency that reflect the intra-axonal distribution and orientation of the white-matter tracts with respect to the applied magnetic field. These metabolite-specific susceptibility effects are also shown to change with age. Results indicate no change of apparent brain temperature with age from 18 to 84 years old, with a trend for increased brain temperature throughout the cerebrum in females relative for males on the order of 0.1 °C; slightly increased temperatures in the left hemisphere relative to the right; and a lower temperature of 0.3 °C in the cerebellum relative to that of cerebral white-matter. This study presents a novel acquisition method for noninvasive measurement of brain temperature that is of potential value for diagnostic purposes and treatment monitoring, while also demonstrating limitations of the measurement due to the confounding effects of tissue susceptibility variations.

Introduction

The temperature of the brain reflects cerebral metabolism and physiology and its non-invasive measurement may be of value as a marker of disease and for monitoring of hyperthermia or hypothermia treatments. However, little is known about normal brain temperature distributions and changes with disease due to the difficulties of performing in vivo brain temperature measurements in human subjects. Several studies have reported on the use of proton MR spectroscopy for temperature measurement, which is based on the temperature dependence of the water resonance frequency of approximately 0.01 ppm/°C. It has also been shown that for studies of the brain the signal from N-acetylaspartate (NAA) provides a convenient frequency reference (Cady et al., 1995; Corbett et al., 1995) and additionally that combining this with frequency measurements from the creatine (Cre) and choline (Cho) resonances may provide greater reproducibility (Cady et al., 2010).

Previous MRS measurements of brain temperature in human subjects have used single-voxel or volume-selected two-dimensional spectroscopic imaging (SI) acquisitions (Cady et al., 2010; Childs et al., 2007; Corbett et al., 1997; Covaciu et al., 2010; Karaszewski et al., 2006), with the result that only a small fraction of the brain volume, which does not include cortical surface regions, has been sampled. In this report a volumetric "whole-brain" SI sequence has been used that samples a much larger brain volume. An additional limitation of previous MRS temperature measurement studies is that the effect of tissue-specific differences in the water resonance frequency were not taken into account. These are known to be caused by differences in magnetic susceptibility, with additional contributions from proton exchange, and result in differences of the water resonance frequency in gray-matter (GM) and white-matter (WM) tissues (Duyn et al., 2007; He and Yablonskiy, 2009). He and Yablonskiy have demonstrated that susceptibility-induced shifts of the water resonance depend on cellular and subcellular organization and it has been proposed by Chadzynski et al. (2011) that shifts of metabolite resonance frequencies occur that similarly depend on the subcellular compartmentalization of each metabolite. With a reported difference in the water-NAA resonance frequency separation of 14 ppb (Chadzynski et al., 2011) this could result in an error in the temperature measurement of up to 1.4 °C. Correction for this tissue composition effect becomes more important when mapping temperature over a larger brain volume; therefore, an additional aim of this study has been to confirm the previous measurements of metabolite-specific frequency shifts between GM and WM and to include this effect in the temperature calculation.

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The water ^{1}H resonance frequency is linearly dependent on temperature; however, the calibration of the slope and intercept of this temperature dependence has proven to be problematic. Several reports have published calibration values based on measurements in phantoms (Cady et al., 1995; Corbett et al., 1995; Covaciu et al., 2010), rat brain (Zhu et al., 2008) and piglet brain (Cady et al., 1995, 2010), however, with little agreement on the calibration values. It has been demonstrated that calibrations in solutions depend on protein and ionic content (Vescovo et al., 2013) and that the spectral fitting (Zhu et al., 2008) and data acquisition (Childs et al., 2007; Prakash et al., 2014) methods can affect the results. The in vivo calibration measurements will additionally be affected by the magnetic susceptibility of the sampled tissue region, which has previously not been taken into account. A related difficulty is validation of the measurements since the true temperature cannot be measured non-invasively in the brain of normal human subjects by any other method. Direct temperature measurements that have been done in the human brain during surgery indicate that temperature increases with depth and that the center is on average approximately 0.5 °C above that of the rectal temperature (Hirashima et al., 1998; Mariak, 2002), and similar findings have been observed in animal studies (Wang et al., 2014; Zhu et al., 2006). However, more detailed information on the distribution of temperature within the brain and possible associations with factors such as age, gender and body weight remain unknown.

This study presents an analysis of volumetric 1H MRSI data obtained from normal adult subjects. By taking advantage of signal averaging following spatial normalization of multiple data sets, improved measurements of the average brain temperature in a group of subjects can be obtained. In addition, the effect of tissue-specific frequency shifts was evaluated and incorporated into an image-based temperature calculation. The spatial variation of brain temperature and associations with subject age, gender, and weight were then examined.

Methods

Subject selection

MRI and MRSI studies of the brain in healthy subjects were obtained from an existing database of 150 studies, aged 18 to 84, with 90 female subjects. These studies were carried out under five research protocols, each of which was approved by the institutional human subjects research review committee and with informed consent obtained from all participants. Results using these normal control data have been previously published (Govind et al., 2010, 2012; Maudsley et al., 2009, 2010a; Sabati et al., 2015). Subjects were screened to exclude any history of brain disease or injury, substance abuse, or psychiatric condition. Eight elderly subjects were screened using neuropsychological test procedures and verified to be cognitively normal, whereas self-reporting procedures were used for all other subjects.

Data acquisition methods

Volumetric MRSI data were acquired at 3 T (Siemens Trio) using a spin-echo acquisition with echo-planar readout, frequency-selective water suppression, lipid inversion nulling, and TE/TR/TI=70/1710/198 ms. Details of the sequence have been previously provided (Ebel et al., 2001; Sabati et al., 2015). Data was sampled with 50×50×18 points over a field of view of 280×280×180 mm, for a nominal voxel volume of 0.313 cc, and with selection of a slab of 135 mm covering the cerebrum. Spectral sampling used 1000 sample points with 2500 Hz spectral width that was reduced to 500 points and 1250 Hz following resampling and combination of the odd and even echoes (Metzger and Hu, 1997). The MRSI acquisition included a second interleaved dataset that was obtained without water suppression and using 20° excitation and gradient-echo observation, and which provided a water reference signal with identical spatial and spectral parameters to the metabolite MRSI. Each study also included a T1-weighted MRI (MPRAGE, Magnetization Prepared Rapid Gradient Echo) at 1-mm isotropic resolution (TR/TE/TI=2150/4.4/1100 ms, flip angle 8°).

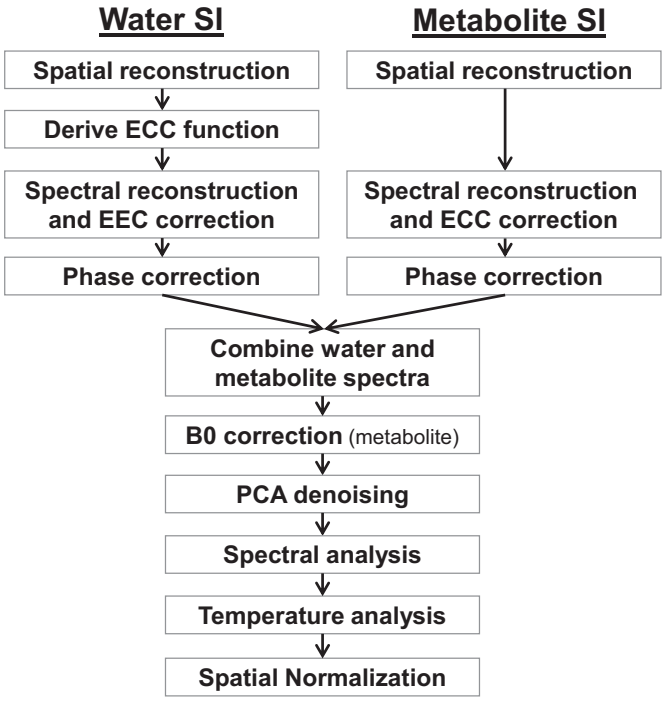

Fig. 1. Summary of the main processing steps for the calculation of the temperature maps. ECC=Eddy Current Correction, PCA=Principal Component Analysis.

Data processing

The metabolite and water-reference MRSI datasets were reconstructed using the MIDAS package (Maudsley et al., 2009; Sabati et al., 2015). The major steps of the processing pipeline that are relevant for mapping of resonance frequencies are illustrated in Fig. 1. Spatial reconstruction included the same smoothing and interpolation to 64×64×32 points applied to both the metabolite SI (SI_{Met}) and the water SI (SI_{H2O}) datasets, resulting in a final spatial resolution of approximately 1 cc. Zerofilling to 1024 points was applied in the spectral domain prior to Fourier transformation, with no apodization applied. To enable analysis of both the water and metabolite frequencies while also accounting for spatially variant B0 inhomogeneity, the SI_{Met} and SI_{H2O} spectra were combined and a single spectral analysis carried out that included the water and metabolite signals. The two spectra were combined by splicing and scaling a region of 100 data points (122 Hz) centered at the water resonance into the corresponding location in the metabolite spectrum. The water resonance was scaled to be comparable in amplitude to the metabolite resonances, as shown in Fig. 2. Because the spectral model used in the analysis program uses a common zero-order phase correction for all peaks it was necessary that both the metabolite and water spectra were accurately phased before combination. Although the correction for time-dependent phase variations (ECC) should result in correctly phased spectra for SI_{H2O}, small phase differences were nevertheless observed that appeared to be associated with small line-shape distortions, particularly at voxels near the edge of the brain, and phase variations are always present in the SI_{Met} spectrum; therefore, a zero-order phase correction was applied to both datasets before the spectral combination step.

Prior to spectral analysis a denoising procedure using principal component analysis (PCA) was applied that results in improved spectral quality with minimal impact on spectral linewidth (Abdoli