PhD ABSTRACT

DEVELOPMENT, OPTIMISATION AND VALIDATION OF AN *IN VIVO* SINGLE-VOXEL MRS QUANTIFICATION SCHEME USING BRAIN TISSUE WATER SIGNAL AS A REFERENCE

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I. Introduction:

Magnetic resonance spectroscopy (MRS) is a means of measuring the chemical composition, often referred to as metabolites, of the human body non-invasively and *in vivo*. It is a research tool mostly used in the investigation of neurological disorders [1]. Since its concentration is reported to be constant most of the time, signal from brain tissue water has been used previously as a reference in the quantification of the metabolites [2].

However, studies aimed at measurement of the total water signal are often confronted with time constraints and patient compliance issues, which consequently impact on the accuracy of the results. The use of average values from the literature, on the other hand, does not resolve these accuracy issues. Meanwhile, there are indications that brain tissue water content could vary widely in certain disease conditions such as in brain tumors and inflammation. In such situations, absolute metabolite quantification using the literature estimates of tissue water content will be inaccurate while the measurement of cerebral water content using the available techniques will be impractical for the patients due to scanning time considerations.

This study thus aimed to develop a suitable in vivo quantification technique of the total brain tissue water signal within relatively tolerable time limits for patients. Aspects of the signal acquisition techniques were validated in psoriasis patients and in functional MRS studies of healthy volunteers.

II. Method and materials:

All experiments were carried out on a 3 T General Electric (GE) MR scanner, using an eight-channel receive-only head coil. Spectra were processed using the Spectroscopy Analysis by GE (SAGE) software package (version 7).

A standard metabolite spectral acquisition on the GE MR scanner acquires some unsuppressed-water spectra at the beginning of a PRESS pulse sequence (varying echo times, *TE* and repetition times, *TR* were used for different experiments in this study). Using the SAGE software package (version 7), the unsuppressed-water and suppressed-water spectra were separated to estimate cerebral water and metabolite concentrations, respectively after adjusting those signals for coil loading, relaxation and partial volume effects.

III. Results and discussion:

Serial phantom and human studies conducted over the research period showed that the precision of the scanner was consistently better than 12% and 26% for *in vitro* and *in vivo* measurements, respectively of water and metabolite spectra.

Voxel position-dependent RF sensitivity profile equations were developed by recording unsuppressed water signals (from a phantom) at varying positions covering the whole volume of the head coil. Using those standard equations, the coordinates of any *in vivo* voxel could be substituted into an appropriate profile equation

to estimate an unsuppressed-water signal area that could be used as a reference signal to quantify brain tissue water content. This cerebral water quantification technique is superior to the previous techniques because it does not require extra unsuppressed-water acquisitions, or corrections for variations in the sensitivity of the head coil as both the *in vivo* and reference signals are acquired from the same voxel position.

The developed referencing technique was subsequently used to accurately quantify cerebral water content in healthy volunteers and in psoriasis patients (for the first time).

In the healthy volunteers, the average water content, WC of frontal brain grey matter, GM was found to be higher than that of white matter, WM (GM/WM WC ± SE = 46.37 ± 2.58/42.86 ± 2.46 mol/kg; p = 0.02); parietal voxels also showed a similar comparison (GM/WM WC ± SE = 37.23 ± 1.70/34.14 ± 2.02 mol/kg; p = 0.03); both findings being consistent with previous reports [2]. Water content measured from five voxel positions in the brain did not show significant variation by one-way ANOVA (p = 0.60); there was also no variation with age ($p > 0.05$) and gender ($p > 0.05$). Water content in the psoriasis patients did not also vary significantly (one-way ANOVA, p = 0.63)

Among five brain metabolites quantified using the cerebral water referencing method, only the mean concentration of creatine, Cr was found to be significantly lower in the frontal GM of the psoriasis patients, PsA compared to healthy controls, HC at baseline (PsA/HC ± SE = 6.34 ± 0.38/7.78 ± 0.38 mM/kg; p = 0.01) and post-TNF-α blockade medication (PsA/HC ± SE = 6.69 ± 0.25/7.78 ± 0.38 mM/kg; p = 0.03). No metabolite changed significantly with medication ($p > 0.05$). The significant change in Cr concentration in psoriasis thus suggests that Cr may not be a reliable denominator in studies of psoriasis that express the metabolite concentrations as ratios.

T1 and T2 relaxation times of cerebral water and the metabolites were measured in the prefrontal GM (*T1/T2* ± SE = 1574 ± 61/147 ± 6 ms) and bilateral hippocampi (*T1/T2* ± SE; left = 1475 ± 68/178 ± 83 ms, right = 1389 ± 58/273 ± 98 ms). These estimates were consistent with reported values; relaxation times for cerebral water were however measured for the first time in those regions. The measured relaxation times were used to correct the water and metabolite signals for relaxation effects in the absolute quantification studies discussed above.

The spectral processing technique was further validated in functional MRS studies focusing on the water peak. While healthy volunteers received a visual stimulus, the resulting BOLD effects on the metabolite and water spectral peaks were recorded, and were found to be comparable to previous reports [3]. For the first time, this study further investigated the impact of temporal resolution (determined by NEX) on the amount of the BOLD signal from cerebral water and metabolites. In a single visual activation paradigm, the BOLD effect resulted in increased water peak area which differed significantly between NEX values of 2 and 8 ($p < 0.01$); this observation also was true for NAA and Glu. The findings thus suggest that temporal resolution of the MRS data could result in significant differences in the results of functional MRS studies.

IV. Conclusion:

This study has developed and implemented a referencing method for quantification of total cerebral water content, suitable as a reference for estimation of brain metabolite concentrations, in vivo. Validation studies show that the technique is appropriate for studies involving both patients and healthy subjects.

References

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