An untargeted metabolomics approach to ultra high field MRS in spinocerebellar ataxia

Uzay Emrah Emir[1,2], Margarida Julià-Sapé[3], Peter Jezzard[1], Diane Hutter[2], Khalaf O Bushara[2], and Gulin Oz[2]

[1]*FMRIB Centre, University of Oxford, Oxford, United Kingdom,* [2]*University of Minnesota, Minneapolis, Minnesota, United States,* [3]*Centro de Investigación Biomédica en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Universitat Autònoma de Barcelona, Cerdanyola del Vallès, Spain*

Introduction

The translation of metabolomics NMR approaches to molecular medicine into *in vivo* ^{1}H MRS allows automatic analysis of unresolved *in vivo* spectra by utilizing pattern recognition processes and machine learning methods (1). Unlike the commonly used MRS quantification tools, untargeted metabolomics approaches do not require any prior knowledge and have been successfully implemented at clinical field strengths (≤ 3T) to identify the characteristic spectral features associated with brain tumors (2) and multiple sclerosis (3). However, the use of untargeted metabolomics approaches at clinical field strengths is limited by insufficient sensitivity and spectral resolution. The advent of ultra-high field (UHF > 3T) MR has improved both sensitivity and resolution of *in vivo* ^{1}H MRS, thereby UHF may facilitate the utilization of untargeted metabolomics approaches to analyze *in vivo* ^{1}H spectra. In this study, we explored the utility of untargeted metabolomics approaches to distinguish subjects with a movement disorder (spinocerebellar ataxia type 1 (SCA1)) from controls and the potential benefits of 7T relative to 3T for this analytic approach.

Methods

Fourteen individuals with early-moderate SCA1 (age 52 ± 11 years, mean ± SD, Scale for the Assessment and Rating of Ataxia (SARA) score (4) = 10 ± 2) and 22 age-matched healthy volunteers (55 ± 16 years, SARA = 0.1 ± 0.2) were studied. Measurements were performed on a clinical 3T (Siemens TIM Trio) scanner and 7T scanner (Siemens). A quadrature transmit surface coil inserted into a 12 channel receive array or a 32 channel receive array with body coil excitation were used at 3T. A 16-channel transceiver array coil (5) and B_1^+ phase shimming (6) were used at 7T. Spectra were acquired from the cerebellar hemisphere (17 x 17 x17 mm^3) using a semi-LASER sequence (TR=5s, TE= 26-28ms, NEX=64) (7). Eddy current correction, reconstruction, zero-order phasing of array coil spectra were carried out by using a reference water spectrum acquired from the same VOI. The residual water resonance was removed using the Hankel-Lanczos singular value decomposition (HLSVD) time-domain selective filtering (8). After transforming the signal to the frequency domain, the baseline offset was subtracted from the spectrum. The normalization of the spectral data vector to the L2-norm was performed based on the data-points in the region [0.5, 4.2] ppm. Finally, the spectral range restricted to [0.5, 4.2] ppm was used as an input to SpectraClassifier 3.1, an automated MRS-based classifier-development system (9). Feature selection was performed with Correlation-based Feature Subset Forward Selection and the resulting features were used as an input to the Fisher Linear Discriminant Analysis (LDA). The number of spectral features selected using correlation analysis was set to 3 (<n/3, where n is the number of cases in the smallest group).

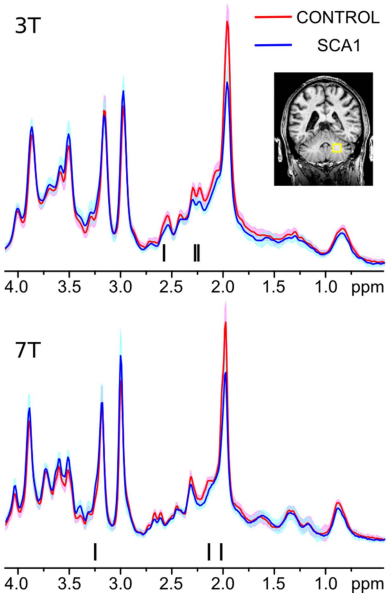

Figure 1. Mean (red and blue)±standard deviation (shade) of normalized ^{1}H MRS from the cerebellar hemisphere of all subjects. Black lines: identified spectral features.

	3T	7T
AUC of CONTROL	1	1
AUC of SCA1	1	1
Spectral Feature 1 (chemical shift, weight)	2.6 ppm, -0.85	2.04 ppm, -3.46
Spectral Feature 2	2.27 ppm, -2.05	3.25 ppm, 7.31
Spectral Feature 3	2.25 ppm, 0.21	2.18 ppm, 1.96

Table 1. Performance estimation and identified features and their weights

Results and Discussion

Figure 1 shows the mean and standard deviation spectra for control and SCA1 groups with three identified features at 3T and 7T. The performance of the LDA classifier judged by the area under curve (AUC), and the identified spectral features and their weights are reported in Table 1. The projection space plot of the LDA classifier showed a distinct clustering with a complete separation between SCA1 and controls at 3T and 7T (Figure 2). LDA projection space results and clinical SARA scores were further used for correlation analysis (Figure 3). LDA scores at 7T showed significant correlation, whereas those at 3T did not. Spectral features identified at both magnetic fields were in agreement with previous findings (10). The improved sensitivity and resolution at 7T enabled the identification of three distinct features whereas only 2 distinct features were identified at 3T, indicating a potential to detect additional spectral features at 7T to distinguish groups. In addition, the potential to predict clinical representation of SCA1 at 7T was demonstrated. While a larger sample size is needed to confirm these findings, this pilot study indicates that increased sensitivity and resolution at 7T may improve the utility of untargeted metabolomics approaches in diagnostic ^{1}H MRS.

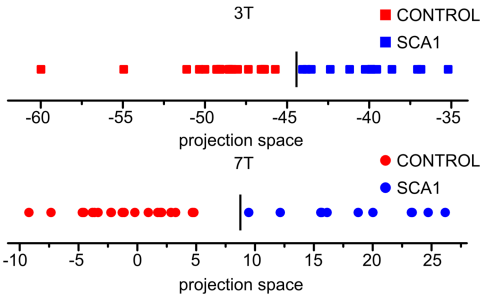

Figure 2. LDA projection space results and boundaries (black vertical lines) of clusters.

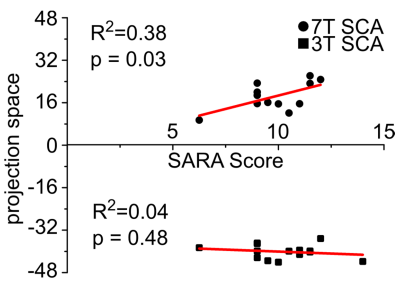

Figure 3. Correlation between LDA scores and SARA scores of SCA1 patients at 3T and 7T

References

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