

## MRS Biomarkers of Neurodegeneration in Spinocerebellar Ataxia type 1 (SCA1): Current and Future Potential

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### Introduction

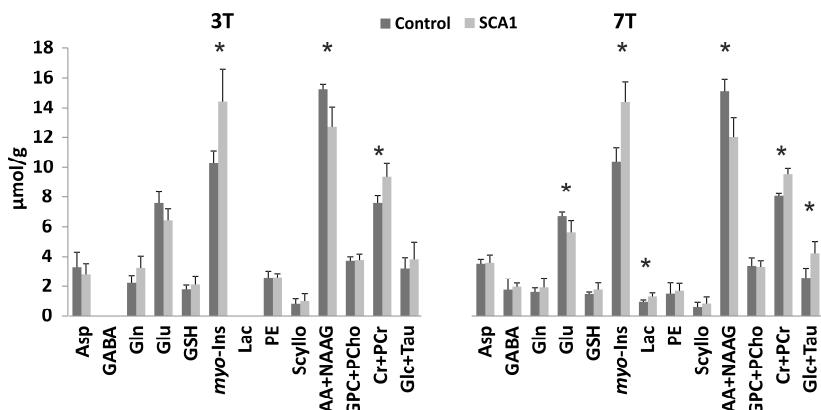
Hereditary spinocerebellar ataxias (SCAs) are movement disorders characterized by loss of cerebellar Purkinje cells in combination with neuronal loss in other regions, such as the pons (1). SCA type 1 (SCA1), a polyglutamine disorder, was the first SCA for which the genetic defect was uncovered (2). As potential treatments for SCA1 enter the pipeline, robust, noninvasive biomarkers of cerebral pathology are urgently needed. A prior MRS study demonstrated neurochemical alterations in SCA1 using a 4T research scanner (3). The goal of the current study was to investigate the current and future potential of this technology on clinical platforms. Therefore, we investigated 1) if similar neurochemical alterations are detectable at 3T using widely available hardware and 2) if increased sensitivity and resolution at 7T enables detection of additional neurochemical alterations.

### Methods

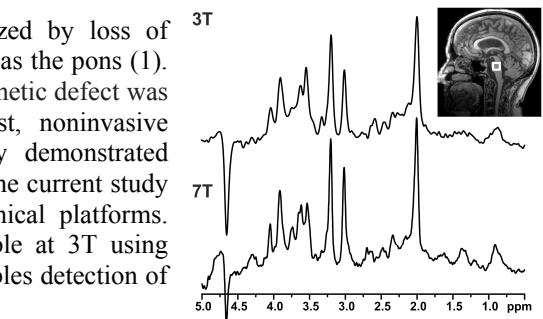
Six individuals with early-moderate SCA1 (age  $47 \pm 12$  years, mean  $\pm$  SD, 5M / 1F, Scale for the Assessment and Rating of Ataxia (SARA) score,  $11 \pm 2$ ) and 5 age-matched healthy volunteers ( $53 \pm 10$  years, 2M / 3F, SARA,  $0.2 \pm 0.4$ ) were studied. Measurements were performed on a clinical 3T (Siemens TIM Trio) scanner and a 7T magnet (Magnex) interfaced to a Siemens console. 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 (4) and  $B_1^+$  phase shimming (5) were used at 7T. Spectra were acquired from the vermis ( $10 \times 25 \times 25 \text{ mm}^3$ ), cerebellar hemisphere ( $17 \times 17 \times 17 \text{ mm}^3$ ) and pons ( $16 \times 16 \times 16 \text{ mm}^3$ ) using a semi-LASER sequence (TR=5s, TE= 26-28ms, NEX=64) with VAPOR water suppression and outer volume saturation (6). Metabolites were quantified with LCModel (7) using the unsuppressed water signal as reference. Only those measured reliably (Cramér-Rao lower bounds (CRLB)  $< 50\%$ , cross correlation coefficients  $r > -0.5$ ) from more than half of the spectra at a given field strength were reported. Concentrations were corrected for the amount of CSF present in each VOI (3) and compared between groups using two-tailed, unpaired t-tests.

### Results and Discussion

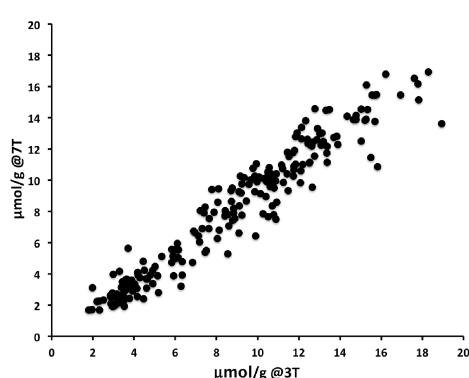
Spectra with good SNR and spectral resolution were consistently obtained from both patients (Fig. 1, data shown from the pons, the most challenging of the 3 VOI for spectral quality) and controls at 3T and 7T. The spectral quality enabled the quantification of a neurochemical profile consisting of 14 metabolites in the vermis and cerebellar hemisphere and 13 in the pons at 7T (Fig. 2), whereas 11, 10, and 11 metabolites were quantified at 3T in the 3 VOI, respectively. Concentrations of major metabolites obtained at 3T and 7T were strongly correlated ( $r = 0.98$ ,  $p < 0.0001$ ) (Fig. 3). Higher *myo*-inositol and total creatine and lower NAA were detected in patients at both magnetic fields, in agreement with previous findings (3). In addition, a potential to detect additional neurochemical alterations at 7T was demonstrated, e.g. in the pons (Fig. 2). While a larger sample size is needed to confirm the findings, these pilot data indicate that 1) prior findings on a research scanner (3) are reproduced on a clinical 3T scanner using an in-house implemented pulse sequence and optimized parameters; 2) increased sensitivity at 7T enables reliable quantification of a higher number of neurochemicals than at 3T and the detection of additional neurochemical alterations.



**Figure 2.** Pontine neurochemical profiles obtained reliably in patients and controls at 3T and 7T. Metabolites that were significantly different between groups are marked with \*  $p \leq 0.05$ . Error bars: inter-subject SD.



**Figure 1.**  $^1\text{H}$  MR spectra obtained with semi-LASER from the pons of one patient with SCA1 at 3T and 7T.



**Figure 3.** Correlation between metabolite concentrations (Glu, Gln, *myo*-Ins, NAA+NAAG, GPC+PCho, Cr+PCr, Glc+Tau) of individual subjects determined from 3T and 7T spectra.

**References:** 1. Taroni F & DiDonato S, *Nat Rev Neurosci*, 5: 641, 2004; 2. Orr HT et al. *Nat Genet* 4:221, 1993; 3. Oz et al. *Mov Disord*, 25:1253, 2010 ; 4. Adriany et al. *MRM*, 59:590, 2008 ; 5. Metzger et al. *MRM*, 59:396, 2008 ; 6. Oz & Tkac *MRM*, 65:901, 2011 ; 7. Provencher SW, *MRM*, 30:672, 1993.

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