Exploring metabolite profiling of patients with secondary progressive multiple sclerosis

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Synopsis

Proton magnetic resonance spectroscopic imaging (MRSI) quantifies brain metabolism in vivo and has the potential of uncovering the mechanism of action of therapeutic drugs. In this study, we assessed the baseline metabolic profile of 161 patients with secondary progressive multiple sclerosis (SPMS) against a control population by applying a short TE PRESS MRSI protocol at 3T. Based on the results the SPMS population could be divided into different groups (normal/biochemically abnormal) suggesting biochemical heterogeneity within SPMS patients.

Introduction

Secondary progressive multiple sclerosis (SPMS) is a highly disabling condition currently untreatable. In order to develop effective therapies for SPMS, a better understanding of the mechanisms underlying its pathophysiology is required. Proton magnetic resonance spectroscopic imaging (MRSI) offers a tool to investigate alteration or preservation of metabolite concentrations. In this study, we explored a novel approach for assessing the metabolic profile of a cohort of SPMS patients enrolled in a single centre multi-arm drug trial, against controls.

Methods

Acquisition: 161 patients (age 55±10yrs) with SPMS (Expanded Disability Status Scale score 4.0-6.5) and 9 healthy controls (HC) (age 48±6yrs) underwent a proton MRSI protocol at 3T (Philips Achieva). A 2-dimensional chemical shift imaging matrix, using short-TE PRESS (TR/TE 2000/35 ms), FOV=210x160mm, 15mm slice, matrix 21x16, 10-minute sequence and 15mL voxels, was acquired through the cerebral hemispheres, with CHESS water suppression.

Data Processing: Data were processed using LCmodel[1] and included N-acetyl aspartate (NAA), Glutamate+glutamine (Glx), Myo-inositol (mIns), total choline (Cho) and total creatine (Cr). Absolute concentrations were found using a water reference scan. Two voxels in the parietal normal appearing white and grey matter (NAWM and NAGM) were selected for each subject (Fig. 1), overlapping the CSI matrix with a corresponding T2w image and taking into account the quality of spectra (peaks shapes, signal to noise ratio>14, FWHM<0.122ppm). The fit of the spectrum was assessed based on the Cramer Rao Lower Bounds values and found to be robust only if CRLB's of reported metabolites were <20%. The mean and standard deviation of the HCs were found in order to help assess deviation from "normal" in the SPMS group.

Analysis: The method establishes the metabolic profile of each SPMS patient, by applying an iterative assessment of each metabolite in turn. Firstly, for each patient i, with i=1 to 161, the NAA ($SPMS_i$) concentration was compared to the (mean±2std) of the NAA(HC) distribution (Fig. 2). In-house software allowed us to assign patient i to either of three groups: 0) NAA($SPMS_i$) < NAA(HC); 1) NAA($SPMS_i$) = NAA(HC); 2) NAA($SPMS_i$) > NAA(HC). This process determined three clusters of patients. The second iteration assessed for each i whether the concentration of the other metabolites (Glx, mIns, Cho, Cr) was within, above or below the mean±2std for the corresponding HCs metabolite. (Fig. 3). Alterations were summarised in table 1, highlighting the presence/absence of subject-specific alterations.

Results

The scatterplot in fig.2 shows the distribution of NAA concentration in SPMS subjects compared to HCs. Patients could be divided into different groups, with metabolic concentrations either close to normal or biochemically altered. Fig 3 shows that within each NAA group (represented by a different colour: group 0 in blue, group 1 in green and group 2 in red) there was a distribution of alterations, with several combinations of normal and altered metabolites. Table 2 summarises the findings of alterations at population level, where NAA and Glx are most likely to be altered in NAWM, mIns, Cho and Cr are altered more often in NAGM.

Discussion

This study presents a novel way to interrogate the metabolic profile of an SPMS population. Despite standard clinical criteria, the metabolic profiles are broad, presumably indicating different pathological evolutions. This evidence is particularly important because it means that SPMS could potentially present different mechanisms of action in different subjects as each metabolite is known to have a main specific role in MS pathology: increased concentration of Glx suggests Glx-mediated cells toxicity[2]; the alteration of mIns can be associated both to a glial cells activation and an attempt of neuronal osmoregulation[3]; NAA is synthesised in neuronal cells and mitochondria and its decrease reflects neuronal loss and energetic dysfunction[4]; Cho can be connected to an active phase of demyelination[5]; and finally Cr can relate to energy storage during mitochondrial failure[6] and to glial proliferation[7]. Potentially, this methodology might predict responsiveness to different drug classes in this trial, where the patients are randomised to one of three different drugs or control over a 2 year period. Further analysis will extend this work to the wider CSI matrix, including tissue-type partial volume correction, and the development of an automatic classification software based on machine learning algorithms to attempt to develop patient-specific MRS profiles.

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Table

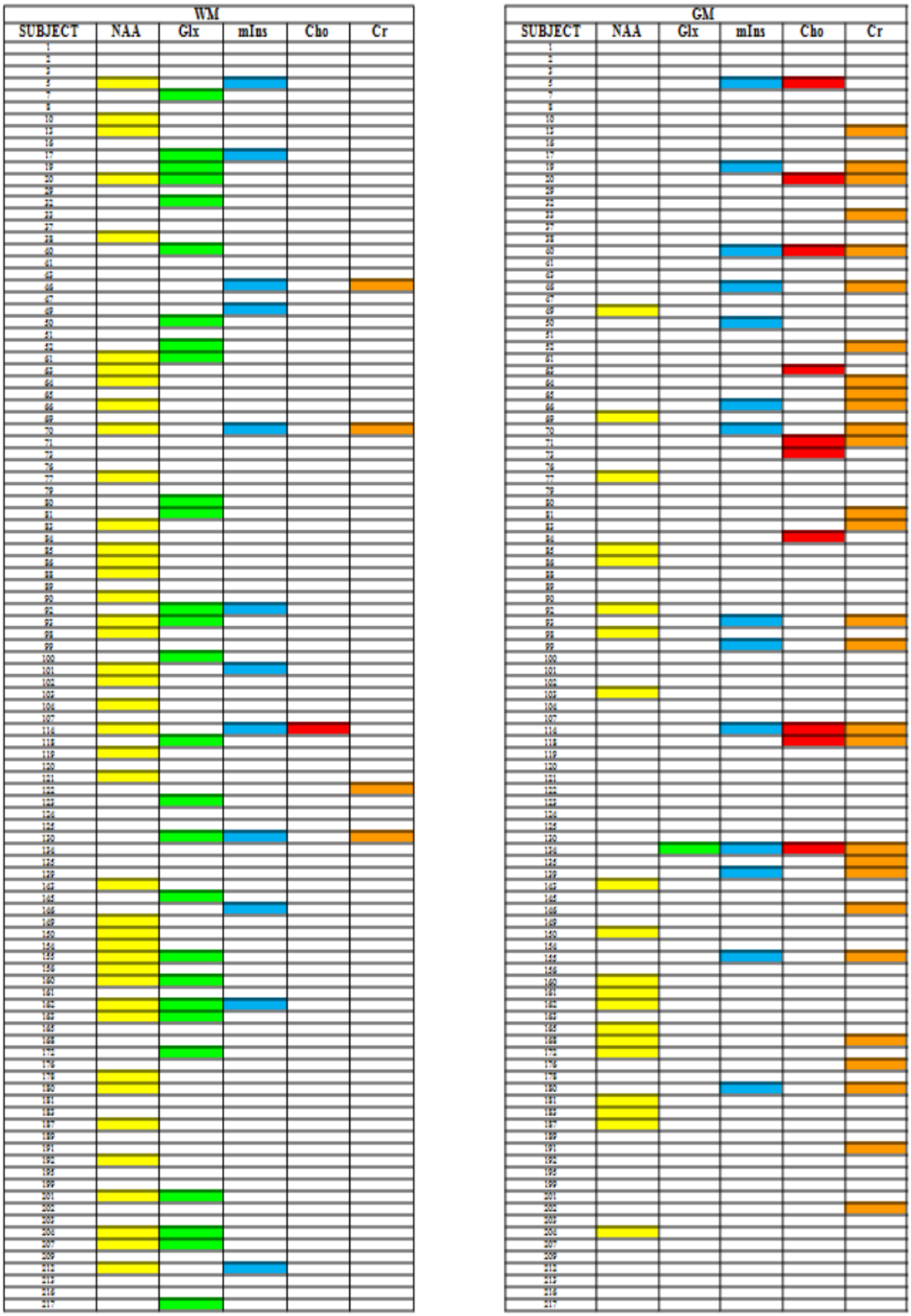

Table 1. This table summarises alterations of NAA, Glx, mIns, Cho and Cr relative to controls: yellow symbolizes the alteration of NAA (41 in NAWM, 20 in NAGM), green Glx alteration (27 in NAWM, 1 in NAGM), blue the alteration of mIns (12 in NAWM, 14 in NAGM), red Cho alteration (1 in NAWM, 10 in NAGM) and orange the alteration of Cr (4 in NAWM, 28 in NAGM). In this way it is possible to understand at a glance for each patient the type of the alterations present in his/her WM (on the left) and GM (on the right).

Figures

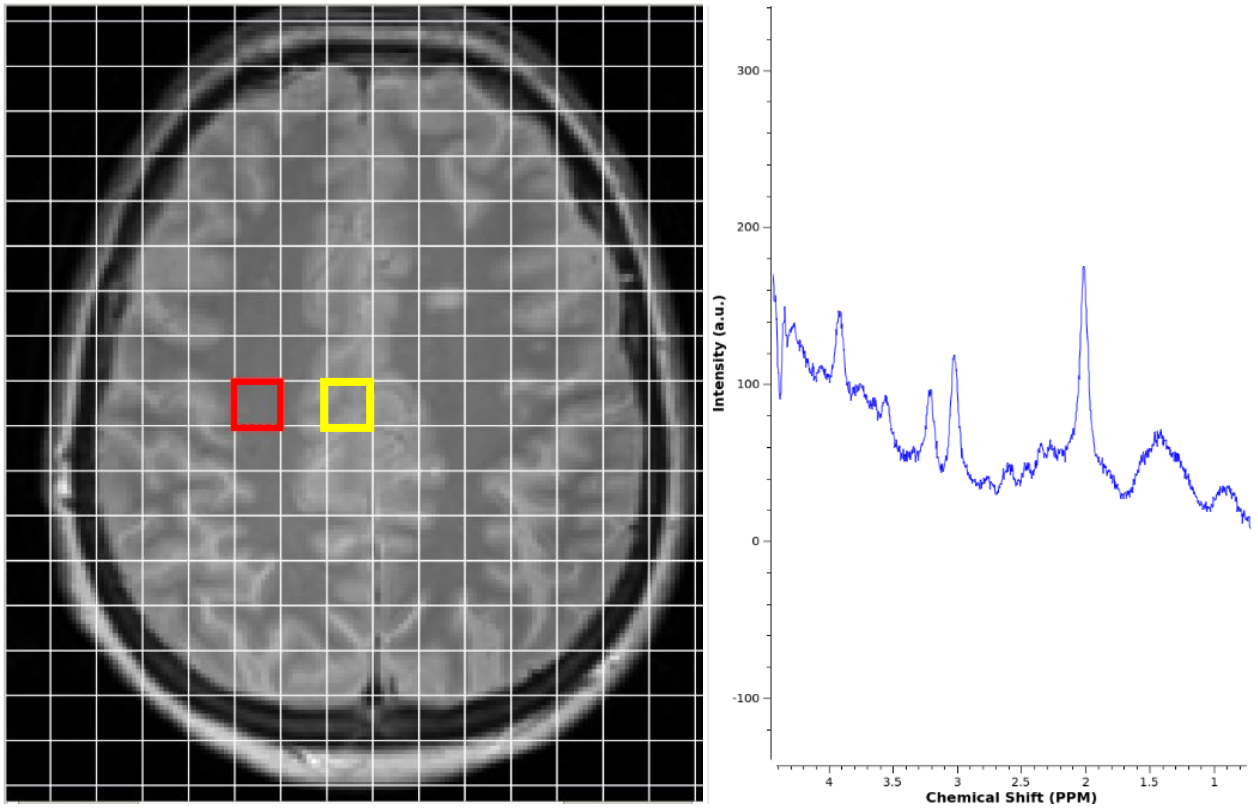

Figure 1. Voxel selection for a representative patient overlapping the CSI matrix with the T2w image. The red box represent the voxel selected for the WM; the yellow box contains the voxel selected for the GM. This image is followed by an example of spectra referred to the WM voxel selected for the same patient that passed the inspection during the voxel selection.

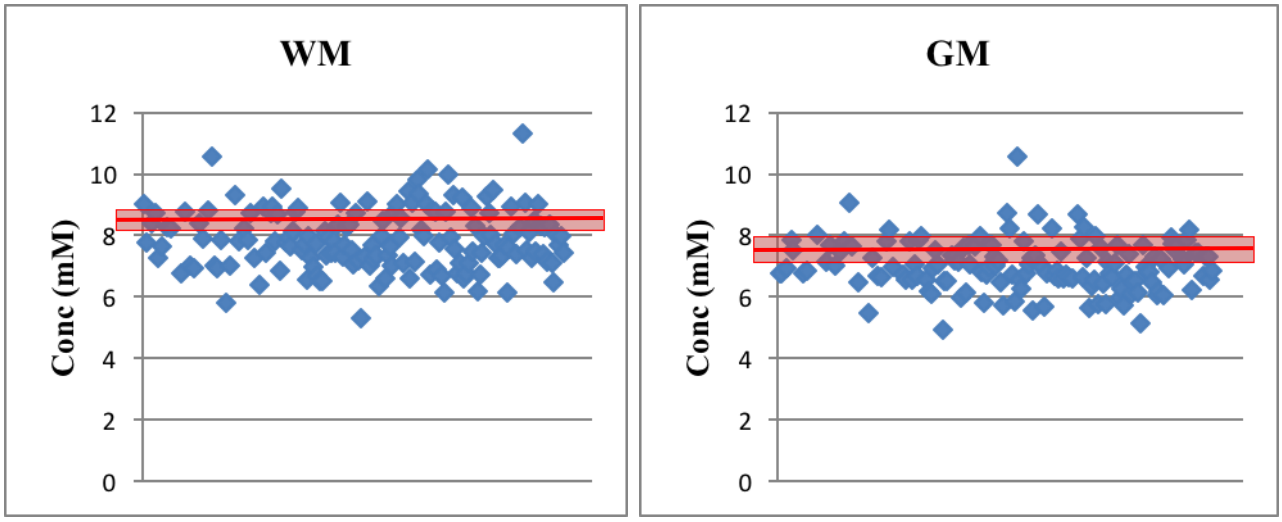

Figure 2. In this figure is represented the overlap of data referred to NAA detected in WM (on the left) and GM (on the right) of patients and controls. The red band represents the range of concentrations detected in controls. Looking at the graph it can be seen that concentrations in patients aren't always altered, but the population can be divided into three different groups: with a concentration higher than normal (above the red band), with a concentration close to normal (overlapped to the red band), with a concentration lower than normal (under the red band).

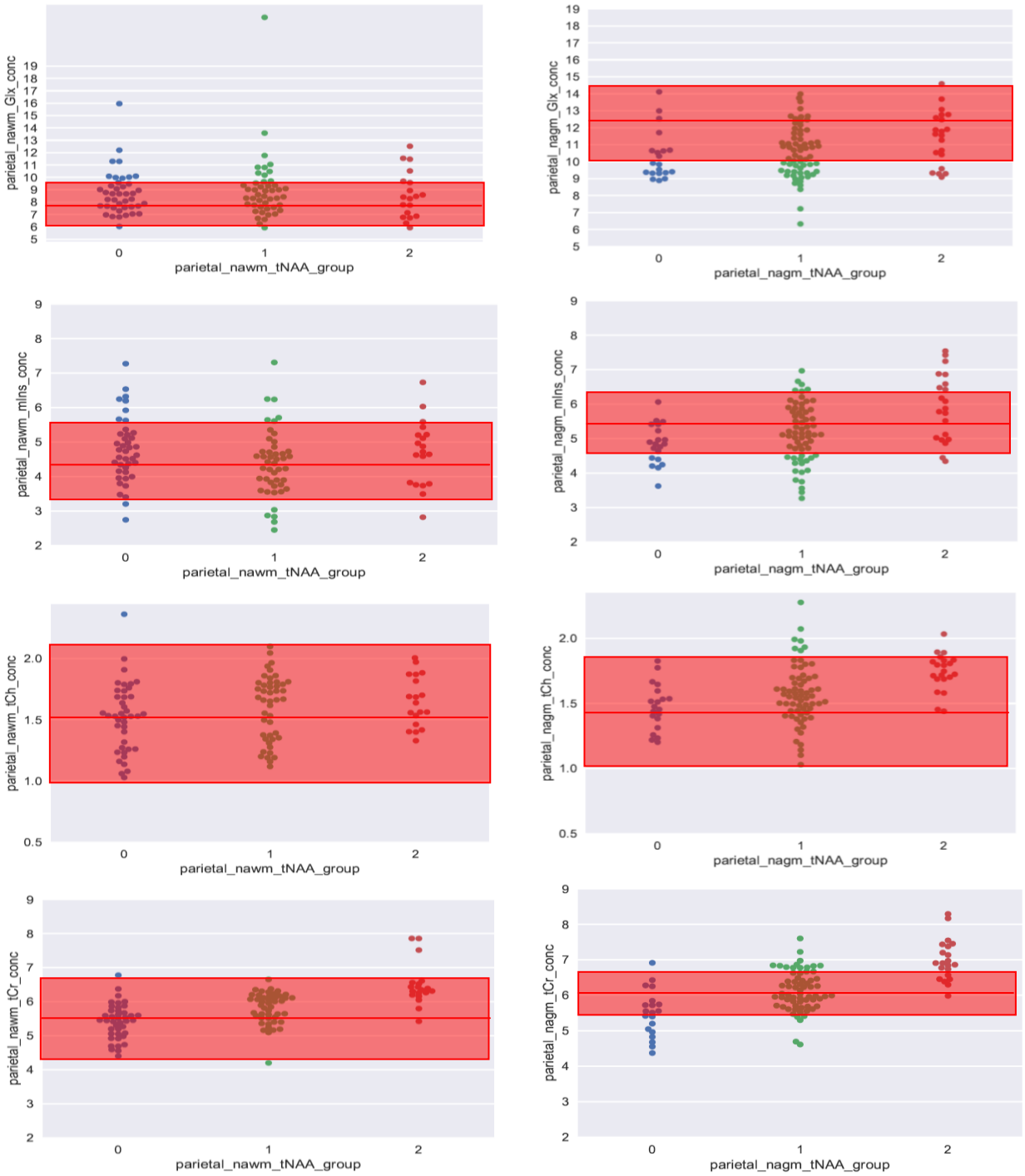

Figure 3. In these scatterplots dots are coloured according to the clusters determined looking at the NAA concentration in patients with respect to controls. Blue represents cluster 0 (NAA< mean±2std of NAA in controls); green represents cluster 1 (NAA= mean±2std of NAA in controls); red represents cluster 2 (NAA> mean±2std of NAA in controls). Dots distribution is determined by the concentrations detected in WM (on the left) and GM (on the right) of a second metabolite positioned on the y axis. The red bar represents the range of concentrations (mean±2std) of the y axis' metabolite detected in controls.

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