Myelin quantification in Magnetic Resonance Imaging

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Abstract— **we can monitor the progression of demyelination by quantifying parameters sensitive to myelin *in vivo* using MRI. g-ratio is an index used to monitor the myelin damage; here we developed a method to calculate g-ratio maps from different myelin-sensitive imaging techniques, i.e. quantitative magnetization transfer (qMT), considered as gold standard, and the T1W/T2W ratio. We compared the clinical sensitivity of the two methods, in a cohort of multiple sclerosis (MS) patients. Both approaches showed a similar trend of myelin damage in pathological subjects.**

*Keywords—***myelin, g-ratio, multiple sclerosis.**

I. INTRODUCTION

MYELIN is a lamellar structure wrapped around the axons of neurons. Since the presence of myelin significantly increases the conduction speed of the signal along the axon, myelin in essential for the transmission of the neuronal signals [1].

Multiple imaging techniques sensitive to the distribution of myelin and its quantity have been developed over time to analyze myelin *in vivo* using magnetic resonance imaging (MRI). Among these techniques, quantitative magnetization transfer (qMT) [2] and the T1W/T2W ratio [3] were used in this study.

g-ratio is an index used to quantify the state of myelin and the signal conduction speed. g-ratio estimates the thickness of the myelin for a certain axon diameter and it is calculated as the ratio between the internal and the external diameter of the myelin sheath.

Myelin thickness is influenced by demyelination and remyelination processes, which impact on the g-ratio values too. In demyelinating diseases such as multiple sclerosis (MS), g-ratio could be used to monitor the evolution of the disease.

In this study we develop an algorithm to obtain g-ratio maps from different imaging techniques and we compared their sensitivity to pathological changes in a cohort of MS patients.

II. METHODS

A. MRI acquisition

Data were acquired using a Philips Ingenia 3T scanner. The protocol included: a diffusion weighted (DW) scan using an EPI spin-echo sequence (TR/TE=6287/96 ms, resolution 2x2x2 mm^3, 3/20/20/36 DW images with b-value=0/1000/2000/2800 s/mm^2), a high-resolution anatomical T1W 3D scan (TR/TE/TI=6.9/3.1/810 ms, resolution 1x1x1 mm^3, flip angle=8°) and a qMT sequence (TR/TE=7626/59 ms, resolution 2x2x2 mm^3, 10 MT weighted and 2 reference images).

B. Subjects

59 subjects were analyzed, of which 17 healthy subjects (HC; 13 females, 57±8 years), 3 relapsing-remitting MS (RRMS; 1 female, 64±3 years), 7 primary progressive MS (PPMS; 2 females, 61±4 years) and 32 secondary progressive MS (SPMS; 21 females, 56±6 years).

C. Images processing

We pre-processed the acquired images to reduce noise and remove artefacts. We obtained: from the qMT images the bound pool fraction (BPF) [4] map, from the Neurite Orientation Dispersion and Density Imaging (NODDI) model [5] the isotropic volume fraction (v_{iso}) and intra-cellular volume fraction (v_{ic}) maps.

D. g-ratio calculation from qMT

MRI-derived metrics, such as the Myelin Volume Fraction (MVF) and the Fiber Volume Fraction (FVF) [6], can be used to calculate the g-ratio *in vivo*.

$$\text{g-ratio} = \sqrt{1 - \frac{MVF}{FVF}} \qquad (1)$$

where $FVF = MVF + (1 - MVF)(1 - v_{iso})v_{ic}$ [7].

The MVF was calculated from the BPF maps and we assumed the g-ratio maps calculated from qMT as the gold standard.

$$MVF = k\, BPF \qquad (2)$$

The constant of proportionality k was estimated from the specific dataset by setting the mean g-ratio value in the forceps major to be equal to 0.7 [8] for 5 HC. The obtained k value was applied to all subjects to calculate g-ratio maps from qMT, called gratio_qMT (Figure 1).
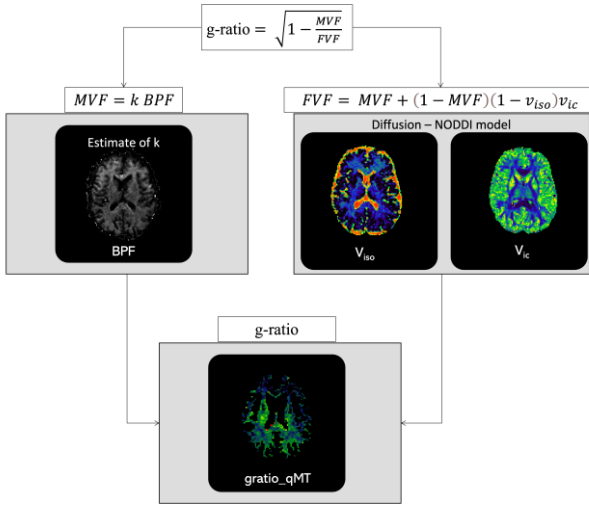
Fig. 1: pipeline for the g-ratio calculation. To calculate the Myelin Volume Fraction (MVF), the constant k for the Bound Pool Fraction (BPF) is estimated. The Fiber Volume Fraction (FVF) is calculated from v_{iso} and v_{ic} of the Neurite Orientation Dispersion and Density Imaging (NODDI) model. g-ratio maps are then obtained from MVF and FVF.
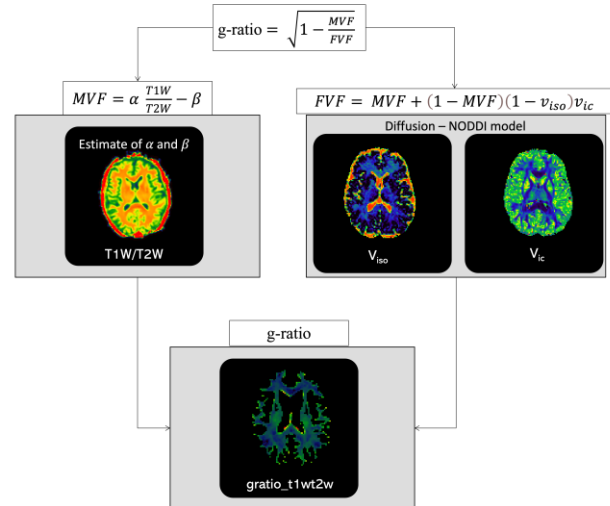

Fig. 3: pipeline for the g-ratio calculation. To calculate the Myelin Volume Fraction (MVF), the constants α and β for the T1W/T2W are estimated. The Fiber Volume Fraction (FVF) is calculated from v_{iso} and v_{ic} of the Neurite Orientation Dispersion and Density Imaging (NODDI) model. g-ratio maps are then obtained from MVF and FVF.

E. g-ratio calculation from T1W/T2W

We developed an innovative way to calculate the MVF, and consequently the g-ratio, from the T1W/T2W ratio. The Ganzetti method (MRtool, [3][9]) was used to obtain the T1W/T2W maps. The DW volume with b-value=0 was used as T2W input.

The existence of a significant relationship between the T1W/T2W ratio and BPF was examined in all the voxel belonging to the corpus callosum (CC). After checking for the presence of a linear relationship between T1W/T2W and BPF, parameters α and β were obtained from a linear regression model. MVF was calculated from the Eq. (3) (Figure 2).

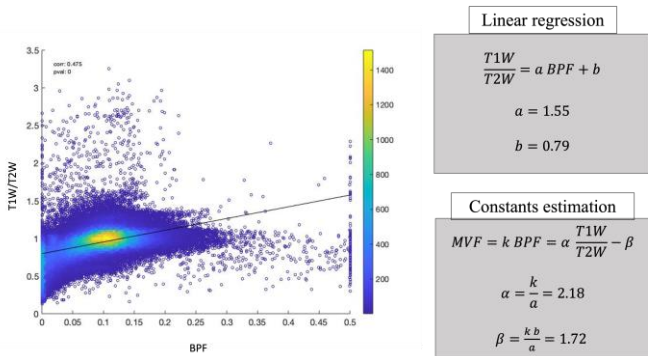$$MVF = \alpha \frac{T1W}{T2W} - \beta \qquad (3)$$

Fig. 2: on the left the linear regression line plotted on all BPF and T1W/T2W data in the corpus callosum. On the right the steps to obtain the constants α and β and the formula to calculate the Myelin Volume Fraction (MVF).

It is thus possible to calculate the map of the g-ratio, called gratio_t1wt2w (Figure 3).

F. Statistics

The g-ratio maps obtained with the two different approaches were compared within-subject for each of the 59 subjects. A Mann-Whitney U-test was performed to compare the g-ratio values of all voxels belonging to the CC.

The clinical sensitivity of the two g-ratio maps was evaluated performing a Mann-Whitney U-test between groups (i.e. HC, PPMS and SPMS). Due to the small sample size, the RRMS patients were not taken into consideration. The statistical evaluation was performed using mean values of the g-ratio in the following regions: white matter (WM), CC, and left and right optic radiations (OR_L, OR_R).

III. RESULTS

The mean value of k resulted 3.39, while α and β were respectively 2.18 and 1.72.

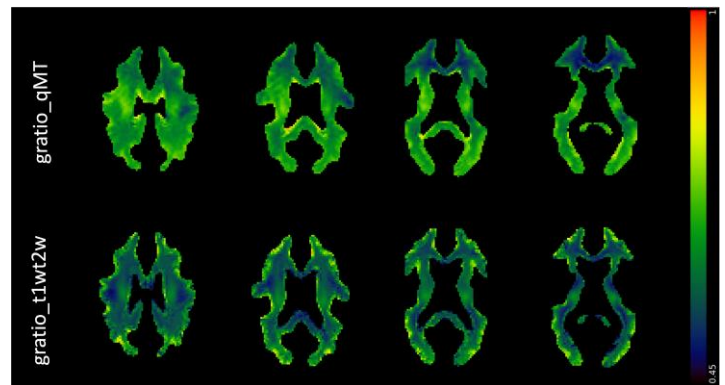Figure 4 shows voxel-wise maps of the mean g-ratio in white matter obtained with the two methods in all HC subjects.

Fig. 4: maps of the mean g-ratio in white matter across all HC subjects. The first row shows the g-ratio obtained from quantitative magnetization transfer (qMT), the second from T1W/T2W ratio.

According to the Mann-Whitney U-test, gratio_qMT and gratio_t1wt2w are statistically different (p<0.05).

Only the gratio_qMT showed significant differences

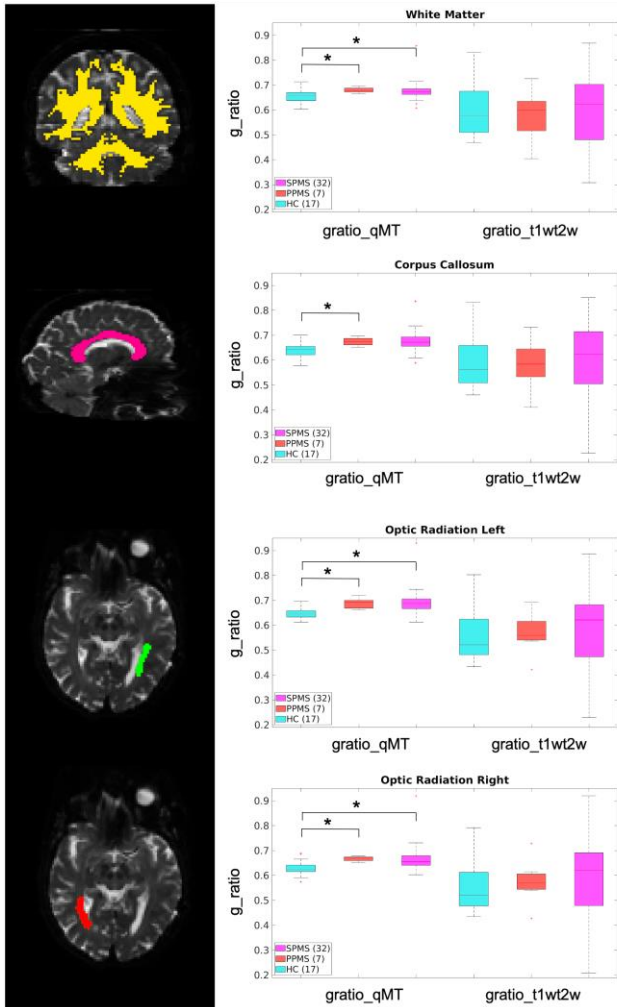(p<0.05) between groups in all the regions of interest (Figure 5).

Fig. 5: boxplot of the mean g-ratio for the three groups investigated; the groups and the number of subjects per group are indicated in the legend (Healthy Control: HC, Primary Progressive Multiple Sclerosis: PPMS, Secondary Progressive Multiple Sclerosis: SPMS). For each group, the mean value of the g-ratio is calculated in the following regions: white matter, corpus callosum, left and right optic radiations. The segmented regions are represented on the left. The asterisk indicates significant differences.

IV. DISCUSSION AND CONCLUSION

According to our findings, there was a difference between the values of gratio_qMT and gratio_t1wt2w. The main cause could be intrinsic to the nature of T1W/T2W images: indeed, T1W/T2W are semi-quantitative maps that are sensitive not only to the state of myelin but also to other pathological conditions, like edema and inflammation. The use of sub-optimal T2W images is another limitation of the gratio_t1wt2w maps.

Moreover, the gratio_qMT maps showed significant differences between HC and MS subjects, which were not replicated by gratio_t1wt2w - the gratio_t1wt2w maintained a similar trend of medians between groups but with a very large standard deviation of values that compromised statistical power (Figure 5). Overall, calculating a g-ratio map with the best available method could help detecting myelin damage in

pathological subjects, highlighting progressive demyelination in patients with advancing MS. Therefore, g-ratio mapping might provide an additional tool to investigate the progression of demyelinating diseases and to evaluate pharmacological approaches to promote remyelination.

In this study we estimated the constant of proportionality k to obtain g-ratio maps from qMT; furthermore we developed a method to calculate g-ratio maps from T1W/T2W, starting from clinical images such as T1W and T2W. Future work can investigate the improvement of this method by using optimal T1W and T2W maps (<1 mm) in particular to see whether the large standard deviation is attributed to the sub-optimal T2W images used here. Finally, gratio_qMT displays a visible difference between the g-ratio of the frontal lobe and the occipital lobe, not seen in gratio_t1wt2w (Figure 4). Given recent publications on the whole brain connectivity, it remains to be determined whether this is biologically plausible and related to a different fiber density in different hemispheres.

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