Quantitative susceptibility of thalamus, basal ganglia and normal appearing white matter in multiple sclerosis

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Synopsis

Quantitative susceptibility mapping is an emerging MRI technique that may provide additional information on brain tissue with potential applications in multiple sclerosis characterization and monitoring. However, the link between tissue susceptibility and disease evolution is not well known. This study investigates the relationship between basal ganglia, thalamus and normal appearing white matter susceptibility and lesion load, based on a fully automated pipeline for lesion and brain segmentation. Significant correlations were found between lesion load and susceptibility in putamen, thalamus, and white matter, presumably due to myelin loss in basal ganglia and iron loss in normal appearing white matter and thalamus.

Introduction

Quantitative susceptibility mapping (QSM) is an emerging technique that can potentially facilitate the characterization of inflammation and demyelination in the brain of multiple sclerosis (MS) patients [1]. In MS, myelin and iron content changes are thought to be the main factors of susceptibility change in the different brain regions and lesions [2, 3]. Thus, QSM is increasingly used for the characterization of iron load in the deep gray matter (DGM) and lesions [4]. Magnetic susceptibility in specific brain regions and lesions might hence be a potential biomarker to monitor disease progression. However, the relation between susceptibility in the brain and the disease state is still not widely investigated. Prior work indicates higher susceptibility for basal ganglia (probably due to demyelination) and lower susceptibility for thalamus and normal appearing white matter (NAWM, probably due to iron loss) with disease progression [5-7]. Moreover, thalamic damage seems to be related to NAWM damage [8]. However, because of technical differences, studies are not fully comparable and conclusive. The goal of this study was to evaluate i) the association between DGM and NAWM susceptibilities, and ii) their relation to disease status based on lesion load.

Methods

We performed a retrospective study on a cohort of 73 (59 women, mean age = 38.5 years, standard deviation = 12 years, range: 17-66 years) MS patients, who underwent a single-time-point brain MRI at 3T (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany). The acquisition protocol included 3D FLAIR, T1-MP-RAGE pre/post-Gd, and double-echo GRE (TE=20/40ms) sequences (relevant acquisition parameters are given in Table 1). The fully automated prototype method LeManPV [9, 10] was used for the segmentation of MS lesions taking 3D FLAIR and T1-MP-RAGE pre-Gd images as input. Brain lobes, and segmentations of NAWM, thalamus, and basal ganglia (putamen, pallidum, and caudate) were obtained using the MorphoBox prototype [11] taking T1-MP-RAGE pre-Gd images as input. QSM maps were estimated from GRE images using a standard post-processing pipeline that incorporates RESHARP and TVSB algorithms [12, 13]. LeMan-PV and MorphoBox output masks were rigidly registered into the QSM space using ELASTIX [14]. Subsequently, median QSM values of thalamus, NAWM, and basal ganglia were extracted (see Figure 1). Since the QSM reconstruction includes an ill-posed inverse problem, it is only possible to quantify magnetic susceptibility in relation to a reference value rather than in absolute terms [15, 16]. To account for this offset, the median QSM value of the frontal and parietal normal appearing NAWM was subtracted from each extracted QSM value of the same patient (except the NAWM itself). Spearman's correlations were evaluated in two scenarios:
i) Lesion load analysis: relation between total lesion volume in each brain lobe and susceptibility in
a. thalamus and NAWM, expecting negative correlation due to decreased iron content.
b. basal ganglia, expecting positive correlation due to decrease in myelin content.
ii) NAWM susceptibility analysis: relation between NAWM and DGM susceptibilities, expecting a positive correlation due to interconnectivity.

Results

From the entire cohort, two patients were excluded due to poor image quality.

i) Lesion load analysis: We found significantly positive correlations between both right and left putamen and the supratentorial lobes (rho = [0.25 to 0.35], p-value = [0.002 to 0.038]) except the right occipital lobe. We found significantly negative correlations between right thalamus and right frontal lobe (rho = -0.25, p-value = 0.04) as well as right thalamus and temporal lobes (rho = -0.32, and p-value = 0.005, see Figures 2). We found strong negative correlations between NAWM susceptibility and lesion load of each region (rho = [-0.55 to -0.78], p-value < 0.0001).

ii) NAWM susceptibility analysis: We found a positive correlation in the right (rho = 0.54, p-value = 0.00001) and left (rho = 0.32, p-value = 0.005) thalami, and a negative correlation in right (rho = -0.29, p-value = 0.012) and left (rho = -0.29, p-value = 0.014) putamen.

Discussion

Comparing lesion load with DGM structures and NAWM susceptibilities, we found that a lower susceptibility of the thalamus and NAWM as well as a higher susceptibility for basal ganglia were associated with higher lesion load. Assuming that lesion load is related to disease duration and disability (although not perfectly correlated), these results are in line with previous studies [7]. Our findings bring more evidence that susceptibility of the studied structures could be used as biomarkers for disease progression (providing information about iron loss in NAWM and thalamus and myelin loss in the basal ganglia. Additionally, we found a positive correlation between NAWM susceptibility and thalamus susceptibility, adding evidence to the interconnectivity of both structures and their association to the damage in MS [8].

Conclusion

In this study, we found several correlations between lesion load per lobe and susceptibility values of the thalamus, NAWM and basal ganglia. From our findings, new biomarkers for disease progression in MS providing information regarding iron and/or myelin loss could potentially be derived which would facilitate personalized treatment planning in the clinical practice.

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Figures

Parameter	*MP-RAGE pre-Gd*	*3D FLAIR 3D*	*Double-echo GRE*
Resolution	1x1x1.2 mm³	0.5x0.5x1 mm³	0.98x0.98x1.5 mm³
Orientation	Sagittal	Sagittal	Transversal
Flip angle	9°	120°	15°
TR/TI	2300/900 ms	5000/1800 ms	46/-
Echo Time	2.9 ms	391 ms	20/40 ms

Table 1 : Acquisition parameters of the three sequences used in this study.

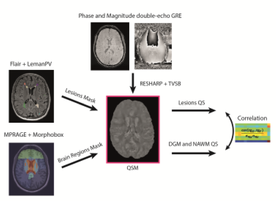

Figure 1 : Schematic representation of different images and algorithms used to a) compute QSM using RESHARP and TVSB on double-echo GRE, b) extract MS lesions using LeManPV from 3D Flair and MPRAGE pre-Gd and c) extract brain regions using MorphoBox from MPRAGE pre-Gd.

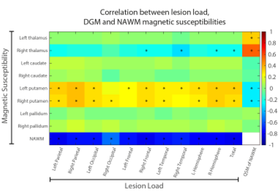

Figure 2 : Spearman correlation coefficient between lesion load and magnetic susceptibility of DGM and NAWM, and between magnetic susceptibility of DGM and NAWM (last column). * indicate p-value < 0.05