Magnetic Susceptibility (QSM) of Thalamic Sub-Nuclear Groups in Multiple Sclerosis

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TARGET AUDIENCE – Researchers interested in new ways of analyzing magnetic susceptibility maps and in the pathophysiologic nature of multiple sclerosis.

PURPOSE – Abnormal accumulation of iron in the brain is known to be associated with several neurodegenerative diseases such as multiple sclerosis and Parkinson's disease. Hence, a major research focus currently lies in developing and applying non-invasive techniques to assess iron concentration in the brain. Quantitative susceptibility mapping[1,2] (QSM) allows assessing the magnetic susceptibility of the bulk tissue, which changes linearly with the average iron concentration in the tissue[3]. While several group-control studies have revealed significant changes of magnetic susceptibility in central nervous system (CNS) diseases associated to changes in either iron or myelin homeostasis, the biophysical and biological cause of these changes remains unclear. Most studies employed relatively coarse automatic segmentation of basal ganglia (BG) nuclei using tools such as FMRIB's Integrated Registration and Segmentation Tool (FIRST)[4] and then compared mean susceptibility values in these regions. Findings resulting from such relatively large regions are questionable because, first, it is well known that basal ganglia nuclei themselves contain several sub-nuclear groups with distinct functions and, second, BG are often relatively inhomogeneous on susceptibility maps. The unique depiction of sub-nuclei on susceptibility maps has recently been exploited to segment the structural divisions of the thalamus in healthy subjects[5]. The various thalamic sub-nuclei have different afferent and efferent connections to other brain regions and represent a major target of current neurological research[6]. In this work we investigate for the first time magnetic susceptibility of the thalamic nuclear groups in patients with multiple sclerosis (MS).

	Pul	MD	VP	VL	VA
HC	95	75	70	70	70
CIS	95	95	95	95	95
RR	95	80	80	80	80
SP	90	**55**	**50**	**50**	**50**

Table 1. Percentage of subjects in which the nuclei could be identified on susceptibility maps.

METHODS – *Subjects:* This study included 20 patients with clinically isolated syndrome (CIS; age 40.6±7.4 yrs, EDSS 1.2±0.9, 1.6±1.7 yrs disease duration, 39±7 yrs at onset) and 40 patients with MS, 20 with relapsing-remitting (RR; age 42.8±7.0 yrs, 2.3±2.1 EDSS, 11±6 yrs disease duration, 31±7 yrs at onset) and 20 with secondary-progressive (SP; age 50.5±5.4 yrs, 5.7±1.8 EDSS, 20±9 yrs disease duration, 30±7 yrs at onset) MS. In addition, 20 healthy controls (HC) without known CNS pathology and without a history of neurologic or psychiatric disorders were recruited (age 46.5±6.2 yrs). These subjects were age-matched to RR-MS (p>0.05) but not to CIS and SP (p<0.05; age: CIS<HC/RR<SP). All four groups (HC, CIS, RR, SP) were sex-matched with 70% females. The study protocol was approved by the local institutional review board, and all participants provided their written informed consent before examination. *Data Acquisition and Processing:* Gradient echo data were acquired on a 3T whole-body MRI scanner (Signa Excite HD 12.0; GE Healthcare, Milwaukee, Wisconsin) with a fully flow-compensated 3D single-echo sequence. The following sequence parameters were used: 64 slices, 0.5x1x2 mm^3 voxel size, 12° flip angle, TE/TR = 22/40 ms; 13.89 kHz BW, 8:46 min:sec. All scans were prescribed parallel to the sub-callosal line in an axial-oblique orientation. Phase aliasing was resolved[10], background fields were eliminated with SHARP[1] (radii 0.5 to 5mm, threshold 0.05), and susceptibility maps were calculated with HEIDI[2]. *Image Analysis:* A trained image analyst visually identified on each susceptibility map the pulvinar (Pul), the medial dorsal nucleus (MD), the ventral posterior nucleus (VP), the ventral lateral nucleus (VL), and the ventral anterior nucleus (VA), the anterior nucleus, and the lateral nuclei. Identified nuclei and the thalamus as a whole were manually outlined bilaterally in 3D using Freeview (FreeSurfer, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA) resulting in up to six 3D regions-of-interest (ROIs) per subject. The analyst was blinded to the patient population. To evaluate the intra-thalamic susceptibility variations, all susceptibility maps were referenced to the susceptibility of the thalamic tissue between the identified nuclei, the internal medullary lamina. We calculated mean values of the susceptibilities in all ROIs using MATLAB (The MathWorks, Natick, MA, USA) and exported the values to SPSS Statistics 22 (IBM Corp., Armonk, NY) for statistical analysis. *Statistical Analysis:* Differences of mean susceptibility values and correlation with age were assessed by means of independent-samples t-test and Pearson correlation coefficient, respectively.

	Pul	MD	VP	VL	VA
HC	0.053±0.022	0.015±0.011	0.019±0.014	0.0076±0.0068	0.0089±0.0081
CIS	0.059±0.012	0.016±0.0096	0.025±0.010	0.0092±0.0075	0.0094±0.0085
RR	0.057±0.015	0.013±0.0094	0.019±0.012	0.0080±0.0070	0.0096±0.010
SP	0.046±0.021	0.0080±0.0097	0.014±0.016	0.0079±0.011	0.0100±0.012

Table 2. Mean and inter-subject standard deviation of magnetic susceptibility values (in ppm) referenced to the magnetic susceptibility of the thalamus between the nuclei.

RESULTS – The anterior nucleus could not be identified in any of the subjects and separation of ventral and lateral nuclei was generally impossible. The number of detected sub-nuclei decreased from CIS over RR and HC to SP in MD, VP, VL, VA (p<0.001, ANOVA) but not Pul (p>0.05) (**Table 1**). The lowest number of nuclei was visible in SP-MS, where MD, VP, VL, and VA were identified in only 50% of the cases. **Figure 1** shows two representative cases along with the ROIs, one with intra-thalamic contrast (left) and one with a homogeneous thalamus (right). Note that the intra-thalamic contrast (on left) is not due to partial volume effects of the sub-adjacent mesencephalon (red nucleus and substantia nigra), but is a true intra-thalamic susceptibility variation. Susceptibility values decreased in the order CIS>RR/HC>SP (**Table 2** and **Figure 2**). Significant differences were detected only between CIS and SP-MS (Pul, MD, VP) and between HC and SP (MD). Combining all subjects, susceptibility values correlated with age only in Pul (R=-0.24, p<0.05) and VP (R=-0.29, p<0.01).

DISCUSSION – This is the first report of varying intra-thalamic tissue contrast. Since we referenced susceptibility maps to the tissue between the nuclei (**Figure 1**, green in insert image on the left), more diamagnetic (lower) susceptibility can be interpreted as a diminishing intra-thalamic susceptibility contrast. This can be explained by either an increase of the magnetic susceptibility in the reference region, e.g., due to redistribution of iron, or a decrease of susceptibility in the thalamic nuclei, e.g., due to iron depletion. The inverse correlation of susceptibility with age as well as the order of decreasing magnetic susceptibility (CIS>RR/HC>SP), resembling the age group-differences (see above), are in line with the known decrease of thalamic iron with age (>35 yrs)[11]. The results indicate that the age-related depletion of iron in the thalamus mainly occurs in Pul and VP. The lack of correlation with age in MD and the relatively low inter-subject variation (**Table 2**) are indicative for disease-related changes (**Figure 2**). Future research will include additional age-matched controls for CIS and SP-MS to disentangle age- and disease-related effects.

CONCLUSION – Visibility of thalamic nuclei on susceptibility maps considerably varies between subjects, with highest visibility in CIS and lowest visibility in SP-MS patients. These results challenge current analysis strategies, which consider basal ganglia nuclei as homogeneous structures. Careful analysis of susceptibility in sub-nuclear groups promises to provide more specific information on pathology-related tissue changes.

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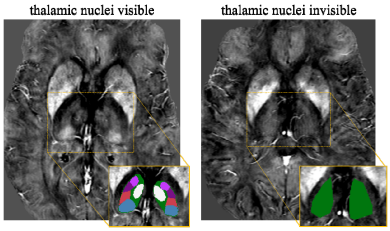

FIGURE 1. Two exemplary cases with visible (left; 43y male, RR-MS, EDSS 2.0) and invisible (right; 53y female, SP-MS, EDSS 7.5) thalamic nuclei, respectively. The small insert pictures illustrate the manual segmentation (blue: Pul, white: MD, red: VP, purple: VL, mauve: VA).

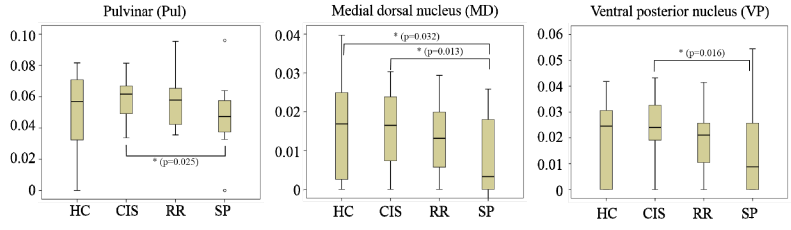

FIGURE 2. Susceptibility values in Pul, MD, and VP of the thalamus. A trend toward lower susceptibility values is visible from HC over CIS and RR to SP. Significant differences are indicated. Susceptibility values were referenced to the internal medullary lamina.