

Structural abnormalities in the thalamus of migraine patients: a multi-parametric study at high field.

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Objective: The thalamus is an important relay of pain processing pathways and exerts a pivotal role in cortical excitability control. A number of works have suggested that thalamic abnormalities may contribute to migraine pathophysiology¹⁻⁷, but so far no study has examined the structural integrity of the thalamus in subjects with and without migraine. The aim of this work was to study the microstructural properties of the thalamus in migraine using a multi-parametric approach at high field MRI.

Methods: We enrolled 22 patients with migraine without aura (MWOA), 15 migraineurs with aura (MWA) and 20 age-matched healthy controls (HC), who underwent MRI scanning in a 3T Trio machine (Siemens, Erlangen, Germany) equipped with a 32 channel coil. The protocol included: MPRAGE (TR/TE = 2400/3 ms, voxel size = 1x1x1.2 mm³, FoV = 256x240x160), MP2RAGE (TR/TE = 5000/3 ms, inversion time = 700 ms, FA = 4°, voxel size = 1x1x1.2 mm³, FoV = 256x240x160), Magnetization transfer (MT, TR/TE = 48/23 ms, voxel size = 2x2x2 mm³, FoV = 240x256x96, 8 echoes) and diffusion spectrum imaging (DSI, TR/TE=6600/138 ms, FoV=212x212 mm, 34 slices, 2.2x2.2x3 mm resolution, 258 diffusion directions, b=8000 s/mm²). T1 maps were derived from the MP2RAGE; MT ratio was computed as follows: $MTR = (M0-MT)/M0 \times 100$; generalized fractional anisotropy (GFA) maps were obtained from DSI using diffusion toolkit (www.trackvis.org) and T2* maps were obtained from the multi-echo MT acquisition. All quantitative maps were linearly registered to the MPRAGE volume using ELASTIX⁸. We performed (i) a ROI-based analysis using an in-house software based on variational expectation-maximization tissue classification⁹⁻¹⁰, and obtained results were compared among groups using parametric ANOVA and Tukey post-hoc test, as well as (ii) voxel-based statistics (non-parametric two-sample permutation test from FSL fmrib.ox.ac.uk/fsl/randomize/index.html). Pearson correlations were performed

between T1, MTR, GFA and SWI values in the thalamus ROI and migraine frequency and duration.

Results: As shown in Fig 1: (i) Mean T1 relaxation time in MWA was significantly shorter than in MWOA patients ($p < 0.001$) and HC ($p < 0.05$) and (ii) Mean MTR was longer in MWA compared to MWOA and HC in both the L and R thalamus but reached significance only when MWA patients were compared to MWOA on the right ($p < 0.05$). Fig 2 indicates that mean GFA and mean T2* did not show any significant differences ($p > 0.1$ and > 0.3). Whole brain statistical maps showed that MWA patients had significantly shorter T1 values compared to HC (figure 3 A-D) and MWOA patients (figure 3 A-D) in numerous thalamic nuclei including the anterior nuclei (an), the latero-dorsal (ld) and medio-dorsal nuclei (md)

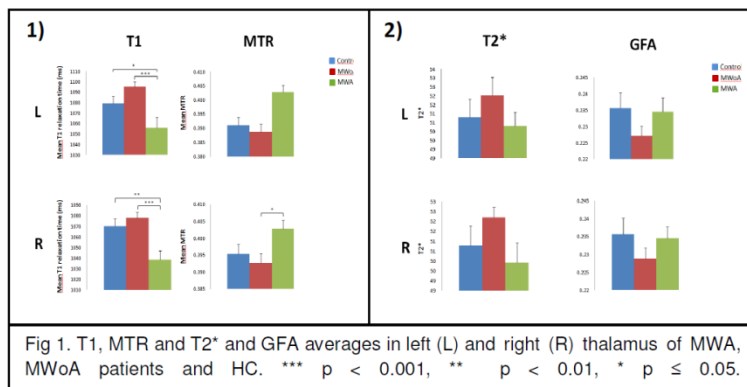


Fig 1. T1, MTR and T2* and GFA averages in left (L) and right (R) thalamus of MWA, MWOA patients and HC. *** $p < 0.001$, ** $p < 0.01$, * $p \leq 0.05$.

as well as the ventro-lateral nucle (vl), ventral-postero-lateral nucleus (vpl) and the posterior group (pulvinar, p and the latero-posterior nucleus, lp). MWA patients showed significantly shorter T1 in the ventral-postero-medial nucleus (vpm) if compared to HC but not with MWOA patients. T2* statistical maps showed slightly higher iron content in only 3 thalamic nuclei (md, p and lp). No significant differences were observed in the whole brain MTR and GFA and no significant correlations were found between T1, MTR and GFA values and migraine frequency and duration in migraineurs. There were no differences in the thalamus volume between migraine patients and HC ($p > 0.1$).

Conclusion: Our study shows that MWA patients exhibit broad thalamic microstructural differences compared to MWOA and HC. Simultaneous T1 and T2* shortening suggest iron deposition as contributor to observed alterations in 3 nuclei; however, in the majority of nuclei, T1 shortening is concomitant to MTR increase without changes in T2* and GFA maps, suggesting that increased density of neuronal or glial cells more than iron deposition and connectivity alterations may be the underlying phenomenon. Future studies may clarify the nature of the observed alterations.

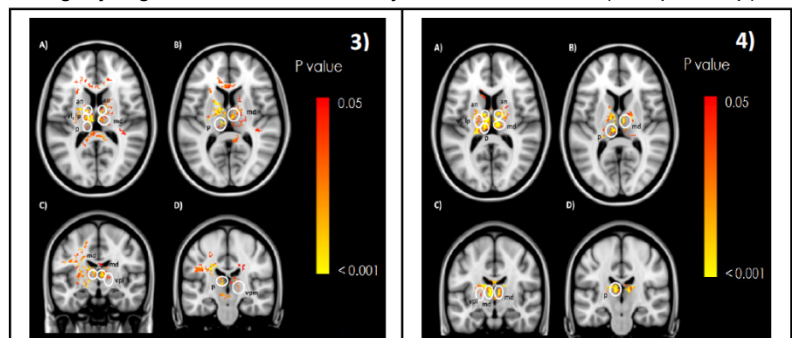


Fig 2: T1 statistical maps of MWA patients vs. HC, showing differences in the thalamus $p < 0.05$. MNI coordinates, an x,y,z : -8, -8, 12; 10, -6, 12; vl: (14, -12, 12); lp: (-14, -18, 12); md: (8, -14, 8; -14, 8; -8, -22, 12; 8, -14, 6); p: (-12, -26, 12; -10, -26, 8; -6, -22, 8); vpl: (16, -14, 4); vpm: (18, -22, 4).

Fig 3: T1 statistical maps of MWA patients vs HC. $p < 0.05$. an (x,y,z : -8 -8 12; -8 -6 12); vl (-18 -14 12); lp (-20, -18, 12); md (6, -12, 8; -4, -12, -10; -6, -14, 8; 8, -14, 8); p -8, -24, 12; -8, -24, 8; -4, -24, 10; -8, -24, 10); vpl: (-20, -14, 6).

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