Distinct Cerebral Tissue Alterations in Diabetic and Hereditary Neuropathic Pain as Revealed by Voxel-based Morphometry and Tract-Based Spatial Statistics

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Purpose:

Neuropathic pain is caused by a lesion or a disease of the somatosensory system itself (1). It's usually more prominent in acquired pathologies of nerve fibers like diabetic neuropathy (DNP) despite less severe degeneration than hereditary neuropathies (HNP). On the basis of differences in etiopathogenetic mechanisms (2, 3), we hypothesized that grey and white matter alterations would reveal distinct patterns in patients with DNP and HNP.

Material and Methods:

IRB was obtained for this study and all the participants gave signed consent form.

Subjects: Eight patients with DNP (M/F: 4/4; 49.71±6.70 years), 6 healthy controls (HC) (M/F: 3/3; 48.17±8.60 years) (t-test; p>0.5) and 6 patients with HNP (M/F:4/2; n:6; 32.00±11.10 years) and 6 HC (M/F:3/3; n:4; 33.50±13.18 years) (t-test; p>0.5) were included in the study.

All patients in each group had diagnosis based on electrophysiological and laboratory studies.

Image Acquisition: All participants underwent MRI on a 3T scanner (Trio, Siemens, Germany). Imaging protocol included T1-weighted 3D high resolution images with 0.9 mm isotropic voxels (MPRAGE) (TR/TE: 1900/3.4 ms; FA: 90; FOV: 256mm; matrix: 224x256; distance factor: %50) and isotropic high resolution DTI of the whole brain (single-shot EPI; TR/TE: 8020 /83 ms, max. b factor: 1000s/mm^2, 60 independent directions, FOV: 256 mm, matrix: 128×128, 64 axial sections with 2 mm thickness without intersection gap, voxel size: 2x2x2 mm).

Data Processing and Analysis

To assess gray matter density, we used VBM protocol using anatomical structure image analysis software FSL-VBM (Smith et al., 2004). Structural images were brain-extracted using BET in order to remove skin and skull. Next, tissue-type segmentation for gray matter, white matter and CSF was carried out with FAST4 package. The resulting gray-matter partial volume images were then aligned to MNI152 standard space using the affine registration tool FLIRT, followed by non-linear registration using FNIRT, which uses a b-spline representation of the registration warp field. The resulting images were averaged to create a study-specific template to reduce the effect of inter-subject brain variability, to which the native gray matter images were then non-linearly registered. The registered partial volume images were modulated using the Jacobian of the warp field and then smoothed with an isotropic Gaussian kernel with a sigma of 4 mm for the threshold free cluster enhanced-based analysis. Differences in cerebral gray matter density between the patient group and control group were determined by voxelwise GLM using non-parametric testing with 5000 permutations. Clusters at $p < 0.05$, fully correcting for multiple comparisons were accepted as significant.

For comparative DTI analysis of the groups, we used tract-based spatial statistics (TBSS), a part of FSL. Preprocessing of the diffusion weighted data including head motion and eddy current correction, diffusion tensor fitting (FSL DTIFit) was performed and fractional anisotropy (FA), and mean diffusivity (MD) were computed. FA maps were registered and aligned to the average space as input for TBSS, and the thinned mean FA skeleton was computed. Then voxelwise statistics were performed using the permutation-based inference with 500 permutations. The resulting TFCE output was corrected for multiple comparisons by controlling the family-wise error rate and thresholded at significance level $p < 0.05$. We used standard cluster-based thresholding corrected for multiple comparisons with a t threshold of 1.5 and obtained the contiguous clusters of supra-threshold voxels using 26-neighbour connectivity.

Results:

VBM:

Patients with DNP: Significantly lower grey matter density in patients with DNP relative to controls was found in bilateral superior temporal gyri, superior parietal lobules, right temporal pole, left inferior frontal gyrus (Broca's area). On the contrary, we found higher grey matter density in the right cerebellum, right motor and pre-central gyrus, prefrontal area, and bilateral insula, occipital lobes and posterior cingulate gyri.

Patients with HNP: Bilateral medial cerebellar, cingulate gyri, left medial thalamus, left pre-central gyrus showed lower grey matter density in patients with HNP compared to controls. We found no region of statistically increased grey matter density in this group of patients.

DTI-TBSS:

Patients with DNP: Major WM alteration was higher FA with a lower MD in the brainstem, splenium of the corpus callosum, left cingulum, optic radiation and right thalamus, right internal and external capsules.

Patients with HNP: Lower FA and higher MD were found in the dorsal brainstem, superior cerebellar peduncles, genu of the corpus callosum, bilateral cingulum and right internal capsule. No significant cluster with decreased FA, increased MD in patients with DNP and increased FA, decreased MD in patients with HNP was observed.

Conclusions:

Grey and white matter alterations revealed distinct patterns in patients with DNP and HNP, as assessed by VBM and DTI. Regions with higher metabolic demand and blood flow may be preferentially affected in DNP.

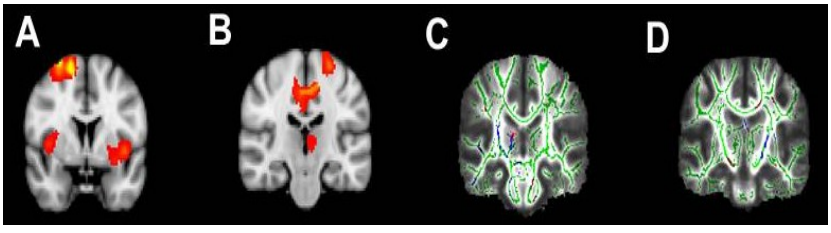

Fig. Slices from the results. A and B :VBM, C and D:TBSS Higher gray matter density in patients with DNP (A) and lower gray matter density in patients with HNP (B) compared to controls. Significant clusters with higher FA (red) and lower MD (blue) in patients with DNP (C), and with lower FA (red) and higher MD (blue) in patients with DNP (D) compared to controls are seen.

References:

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