Novel Robust Segmentation of the Thalamic Nuclei – Validation on Healthy Subjects and Patients

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INTRODUCTION: As a central relay station in the brain, the thalamus is a key region in the cortical-subcortical connections pathway. It is characterized by a complex anatomical architecture composed of several nuclei showing specific characteristics and connections[1]. These regions mediate the involvement of the thalamus in a wide range of neurological functions. Consequently, the study of the thalamic nuclei is of key importance in many neurodevelopmental and neurodegenerative disorders and moreover, their accurate delineation is crucial for a large number of clinical studies and therapeutic approaches such as Deep Brain Stimulation (DBS) or Gamma Knife Surgery (GKS).

PURPOSE: Existing approaches for the automated segmentation of the thalamic nuclei mainly use Diffusion Weighted Imaging (DWI)[2-6]. A major limitation of most existing techniques is that they rely on coarse diffusion features based on low number of diffusion gradient directions[2,3,5]. Moreover, the proposed methods are tested on a low number of subjects[2,4] and limited number of nuclei[6], weakening the robustness of the results and/or their practical use. Additionally, the lack of reliable ground-truth for validation remains an open question. Our study aims to overcome these limitations. We present a novel method for thalamic nuclei segmentation and we validate it in 33 healthy subjects and in 2 patients treated by GKS for essential tremor where the targeted area of the thalamus (e.g. the Ventral intermediate nucleus, Vim) is used as gold standard for validation.

MATERIALS AND METHODS: MR imaging was acquired from 33 healthy subjects and 2 patients treated for essential tremor with GKS having as a target the Vim, which acts as a relay in the motor control system. The GKS target was defined using the quadrilatere of Guiot[7].

The dataset of the healthy subjects is acquired with 3T TimTrio Siemens scanner using the following parameters: MPRAGE (3DGE T1w) with TR/TE=2300/2.98ms, isotropic voxel-size: 1mm^3, 160 slices and DWI with 64 gradient directions, b-value =1000 s/mm^2, voxel-size: 2x2x2.5mm^3, 52 slices. MR acquisitions for the two patients included: pre-operative MPRAGE obtained with 1.5T Aera SIEMENS, TR/TE=1910/3.01 ms, isotropic voxel-size: 1mm^3, 176 slices; post-operative MPRAGE acquired with 3T Skyra SIEMENS using TR/TE=1900/2.95 ms, isotropic voxel-size: 1mm^3, 192 slices; and pre-operative DWI sequence obtained with 3T TimTrio Siemens scanner, 72 gradient directions, b-value=1000 s/mm^2, voxel size: 2.24x2.24x2.2mm^3, 52 slices.

The thalamus masks were first delineated automatically on the T1w images using the atlas-based registration technique provided by the software FreeSurfer[8] and then manually refined in the diffusion space. Our segmentation method is based on the Orientation Distribution Functions (ODFs) represented in the Spherical Harmonics (SH) basis. Such feature provide better angular and shape representation of the diffusion properties as compared to other local diffusion features used so far in the literature. We applied a k-means clustering of the thalamus based on the combination between the spatial distance of voxel coordinates and the distance of the SH coefficients[9]. We worked with a SH basis of order 6 (28 coefficients) and we equally weighted the contribution of each distance metric, spatial and SH. The number of clusters was empirically set to 7, while the initial centroids were defined as the average of the resulting centroids from 5000 randomly initialized k-means clustering. At the end, by employing the Wilcoxon signed-rank test, the resulting clusters were quantitatively compared across subjects and hemispheres.

RESULTS: Evaluation by visual inspection of an expert neuroradiologist highlighted the same pattern along all 35 subjects (controls and patients) and supports the high robustness of our method (see figure 1). **Healthy subjects**: Specific visual inspection of extent and spatial distribution of the clusters on each subject confirmed the similarity with the histological atlas of Morel[10]. Our clustering method results in the following thalamic groups: Anterior (A), Medial-Dorsal (MD), Ventral-Anterior (VA), Ventral-Lateral-Dorsal (VLD), Ventral-Lateral-Ventral (VLV), Ventral- Posterior-Lateral (VPL) and Pulvinar (Pu). Quantitative measures of clusters size and position confirmed the reproducibility of the results showing no statistical differences across subjects and hemispheres (p-values > 0.05). **Patients**: The clustering procedure on the pre-operative data gave equivalent results as in the control subjects. Additionally, on their follow-up T1w images, we could observe a small area of contrast-enhancement corresponding to the therapeutic target used in GKS (e.g.Vim), which belongs to the VLV nuclei group. As depicted in figure 2, this target is included in the pre-surgery VLV delineated by our clustering method (red contour).

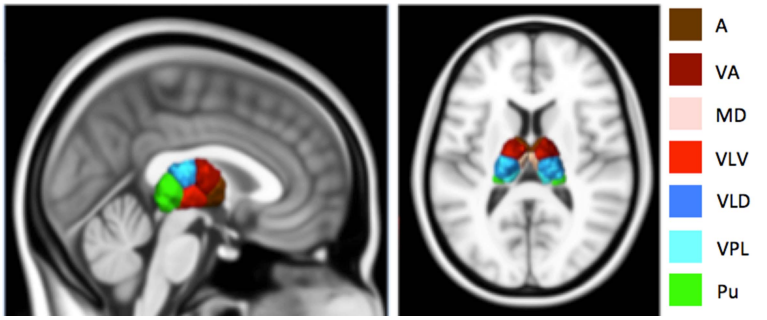

Figure 1: Average image of the resulting clustering among all 33 healthy subjects

DISCUSSION & CONCLUSION: We propose a novel robust method for segmenting the thalamus in 7 anatomical groups based on diffusion MRI and exploitation of local tissue properties at high angular resolution as given by the SH representation of the ODFs. The robustness of the clustering pattern on 33 subjects and the anatomical identification of each segmented group validate qualitatively the results produced by our method. The same pattern was reproducible also in two patients data acquired before GKS. The localization of the GKS target on the follow-up T1w images has been used as a gold standard for the validation of VLV cluster's emplacement. The contrast enhancement corresponding to the targeted area was always localized inside the expected cluster, providing strong evidence of the VLV segmentation accuracy. The development and the validation of this approach already facilitate the study of the effects of several pathologies affecting specific thalamo-cortical pathways and we expect that further development towards a higher resolution and sub-group specificity might then support functional neurosurgical targeting.

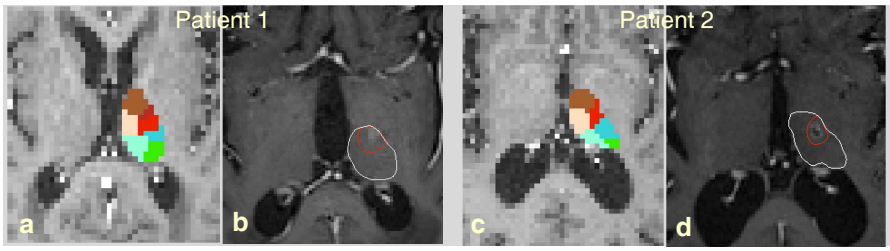

Figure 2: Segmentation outcome for the 2 GKS treated patients. *Panels **a** and **c** show the automated-clustering results for both patients respectively, while **b** and **d** illustrate the contours of the thalamus (in white) and the automatically segmented VLV cluster (in red) superimposed on the one-year follow-up T1w image. As we can see, the small contrast enhancement area corresponding to the GKS target is always inside the automatically segmented VLV.*

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