A NEW APPROACH FOR CEREBELLO-THALAMIC MOTOR NETWORK EVALUATION IN ASYMPTOMATIC PREMUTATION CARRIERS AT RISK FOR FXTAS

Giovanni Battistella[1], Naghmeh Ghazaleh[1], Eleonora Fornari[1+2], Elena Najdenovska[3+1+4], Meritxell Bach Cuadra[1+2+4], Sébastien Jacquemont[5], Philippe Maeder[1]

[1]Department of Radiology, [2]CIBM, [3]Department of Neurosurgery, [5]Department of Genetics
Centre Hospitalier Universitaire Vaudois and University of Lausanne, SWITZERLAND
[4]Signal Processing Laboratory Ecole Polythecnique Fédérale de Lausanne, SWITZERLAND

giovanni.battistella@chuv.ch

Purpose

Fragile-X tremor/ataxia syndrome (FXTAS) is a late onset movement disorder affecting FMR1 premutation carriers (Jacquemont et al., 2003). In our recent work (Battistella et al., 2013, Fig.1) we demonstrated a unique pattern of preclinical changes in young asymptomatic carriers involving part of the cerebellar motor network. However, the approach used could not assess the specific thalamic nuclei involved in motor control that are affected by FXTAS.

We propose to further investigate the cerebellar-thalamic network by:

1. **Developing a methodology to obtain a proper segmentation of the thalamic nuclei, in particular the Ventral Intermediate Medial (VIM) nucleus, a central relay in the motor loop;**
2. **reconstructing the fibers of the dento-rubro thalamic pathway;**
3. **investigating the integrity of this network in premutation carriers by diffusion-derived measures.**

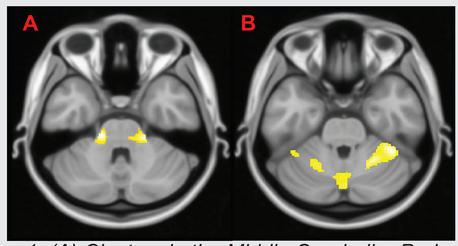

Figure 1. (A) Clusters in the Middle Cerebellar Peduncles showing increased radial diffusivity in carriers. (B)Regions of decrease grey matter volume in carriers compared to controls (lobule VI and vermis).

Acquisition protocol

MR scanning was performed on a 3T Siemens Trio equipped with a 32 channels head coil. Protocol included: sagittal T1-weighted gradient echo sequence (MPRAGE); Diffusion-weighted single-shot EPI sequence (b-value=1000s/mm2, 64 diffusion directions).

1- Thalamus segmentation and clustering

For each subject (35 controls and 27 age-matched premutation carriers) we segmented the thalamus using the Freesurfer software.

Clustering was performed using a constraint k-means algorithm. The distance metric was built estimating the distribution of fiber orientations through the Orientation Distribution Function (ODF, Qboot tool available in FSL).

$$D = \sqrt{\sum_{j=1}^{R} (c_j - c_{j+1})^2}$$

c = Coefficients of the Spherical Harmonics.
R = number of terms in the SH basis.

Inputs: Fractional Anisotropy, and voxel position.
Initialization: centroids of the nuclei in the FSL Thalamic Connectivity Atlas.
Number of clusters set to 7.

Validation over the 62 subjects was performed by a neuroradiologist (Figure 2).

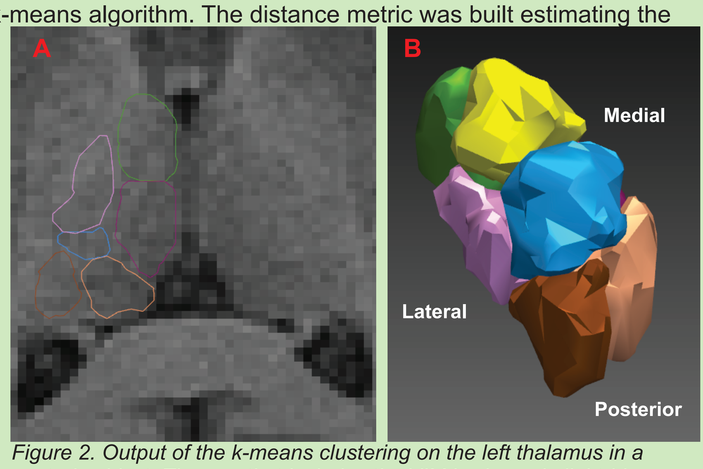

Figure 2. Output of the k-means clustering on the left thalamus in a control subject. The one that includes the VIM is shown in light-blue. Results are shown in an axial view (A), and rendered (B).

2- Fibers reconstruction

Probabilistic tractography using FSL.
Seed masks: thalamus nucleus containing the VIM, the Red Nucleus, and the controlateral Superior Cerebellar Peduncle (Figure 3).
7000 streamline samples, 0.5mm step lenght, 0.2 curvature threshold.

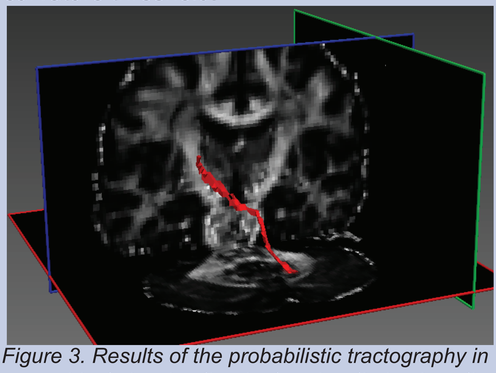

Figure 3. Results of the probabilistic tractography in one subject showing the dento-rubro-thalamic pathway.

3- Application to FXTAS

Voxel-based analysis between controls and premutation carriers along the reconstructed path (step 2) using diffusion-derived measures: Fractional Anisotropy (FA), Mean Diffusivity (MD), radial (RD), and axial diffuisivities. The RD is the most sensitive parameter in detecting alterations in part of the network (Figure 4).

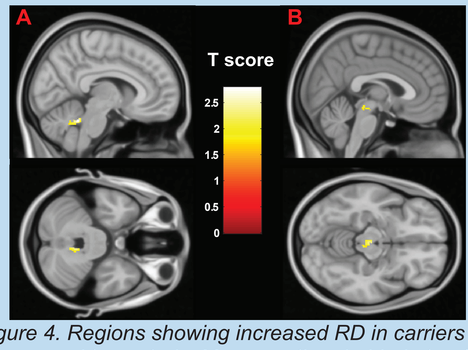

Figure 4. Regions showing increased RD in carriers comnpared to controls. Maps are thresholded at p<0.05

Conclusion

- The clustering of the thalamic nuclei is consistent across subjects and anatomically reliable.
- The reconstruction of the dento-rubro-thalamic pathway is satisfactory in all subjects. The tractography also identifies in the lateral cluster of the thalamus chose as seed, only the part corresponding to the VIM.
- We show alteration of diffusivity properties in part of the network in young asymptomatic premutation carriers.
- The method can be generalised to other disorders and7or pre surgical planning

References

Avec le soutien de: