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

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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.

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).

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

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

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 diffusivities. The RD is the most sensitive parameter in detecting alterations in part of the network (Figure 4).

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 and for pre surgical planning.

References

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).

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).

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).

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

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

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