Contralateral cerebello-thalamo-cortical pathways with prominent involvement of associative areas in humans in vivo

Fulvia Palesi[1,2], Donald Tournier[3,4], Fernando Calamante[3,4], Nils Muhlert[5,6], Gloria Castellazzi[2,7], Declan Chard[5,8], Egidio D'Angelo[2,9], and Claudia A. M. Wheeler-Kingshott[5]

[1]Department of Physics, University of Pavia, Pavia, Pavia, Italy, [2]Brain Connectivity Center, National Neurological Institute C. Mondino, Pavia, Pavia, Italy, [3]The Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, Heidelberg, Australia, [4]Department of Medicine, Austin Health and Northern Health, University of Melbourne, Heidelberg, Australia, [5]NMR Research Unit, Department of Neuroinflammation, Queen Square MS Centre, UCL Institute of Neurology, London, United Kingdom, [6]Department of Psychology, Cardiff University, Cardiff, United Kingdom, [7]Department of Industrial and Information Engineering, University of Pavia, Pavia, Italy, [8]National Institute for Health Research, UCLH Biomedical Research Centre, London, United Kingdom, [9]Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy

Target Audience: Clinicians and physicists with an interest in brain structure and function.

Purpose: In addition to motor functions, growing evidence indicates that in humans the cerebellum plays a significant role in cognition. This is thought to occur through connections with associative areas in the cerebral cortex via synapsis in the thalamus. Classical anatomy indicates that the cerebellum is connected with the contralateral cerebral cortex through the superior cerebellar peduncle (SCP), red nucleus (RN) and thalamus. The anatomical existence of these connections has only been demonstrated using virus retrograde transport techniques in monkeys and rats *ex vivo* [1]. While recognizing that tractography provides only an indirect evidence of anatomical connectivity between regions, using advanced diffusion MRI tractography [2] we aimed at assessing whether (i) the proportion of streamlines reaching corresponding areas of the cerebellar and cerebral cortex are consistent between regions and whether (ii) the majority of streamlines passing through the SCP connects the cerebellar hemisphere with contralateral associative areas.

Methods: MRI acquisition: We performed High Angular Resolution Diffusion Imaging (HARDI) scans on 15 healthy controls (HC) (mean age 36.1 yrs, 8 females and 7 males) using a Philips Achieva 3T MRI scanner (Philips Healthcare, Best, Netherlands) with a 32-channel head coil. All data were acquired using a cardiac-gated SE-EPI sequence. The imaging parameters were: TR=24 s [depending on the cardiac rate], TE=68 ms, SENSE factor=3.1, 72 axial slices with no gap, acquisition matrix=96×112, reconstruction matrix=112×112, 2 mm isotropic voxel, 7 images with b=0 and 61 optimised non-collinear diffusion weighted images with b=1200 s/mm^2 [3]. Diffusion analysis: HARDI data were analysed using FSL[4] and MRtrix[2] with a processing pipeline previously presented [5]. Whole brain tractography was performed with MRtrix by using an algorithm combining the Constrained Spherical Deconvolution (CSD) technique with probabilistic tractography (seed=whole brain, step-size=0.1 mm, maximum harmonics order=8, 2500000 tracks). From these tracks, a Track Density Imaging (TDI) map at 1 mm resolution was created as the total number of tracks passing within each element of the grid. Cerebello-thalamo-cortical tracts were reconstructed by tracking the bundle passing through two regions of interest (ROIs): the SCP and the whole contralateral RN for each hemisphere drawn on the TDI map. Data were normalized to the MNI-152 template by using a non-linear transformation algorithm (FNIRT [6]). To assess the consistency of the pathway, the tracts from all subjects were normalized and a mean/thresholded (10% of subjects) image was calculated from the binarised tracts for each subject in MNI space. In order to assess involvements of different cortical regions, Brodmann and SUIT atlases were aligned to each subject's native space by inverting the normalization transformation. Cerebral and cerebellar cortices were parcellated according to anatomical and functional basis by referring to Brodmann and SUIT. A new index, *"grey matter tract percentage" (T%gm),* was introduced to reflect the percentage of grey matter tract volume in one cortical parcellation *(gmVtract)* compared to the overall grey matter tract volume *(TOT):*

$$T\%gm = \frac{gmVtract}{TOT} \cdot 100$$

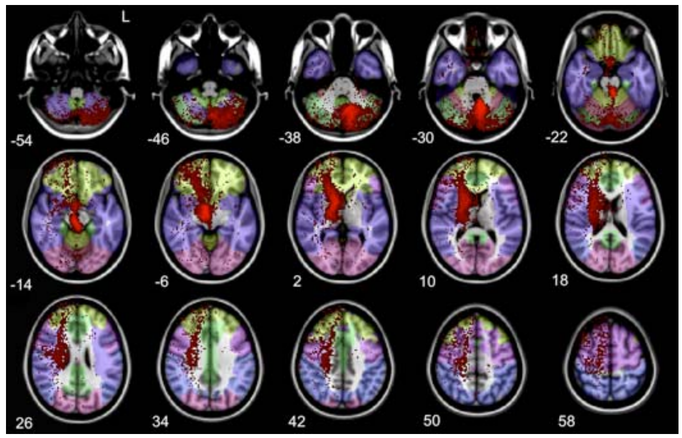

Figure 1: *Left mean cerebello-thalamo-cortical tract in MNI space. Numbers correspond to the z coordinate (in mm). Note fibre crossing below the thalamus (-14 mm) and prominent fibre density in the prefrontal cortex.*

	Anatomical Areas	T%gm	Functional Areas	T%gm
Cerebrum	Prefrontal Cortex	**38 (11)**	Motor Area	14 (5)
	Frontal Lobe	16 (5)	Associative Areas	**80 (8)**
	Parietal Lobe	4 (2)	Primary Somato-sensory	2 (1)
	Temporal Lobe	35 (5)	Primary Visual Area	3 (3)
	Occipital Lobe	3 (3)	Primary Auditory Area	1 (1)
	Limbic Lobe	3 (1)		
Cerebellum	Anter Lobule (I-V)	4 (1)	Primary Motor Area	4 (1)
	Lobule VI	10 (3)	Cognitive/Sensory Area	**79 (4)**
	Lateral Crus I-II	**48 (4)**	Sensory-Motor Area	17 (3)
	Lobules VIIb/VIII	31 (5)		
	Infer Lobule (IX-X)	5 (3)		

Table 1: *T%gm in anatomical and functional parcellations. Data are expressed as mean (SD) for each area. Left and right measurers were averaged together. Note high congruent T%gm in the cognitive areas of cerebellum and neocortex.*

Results: The combined use of CSD and probabilistic tractography successfully reconstructed contralateral cerebello-thalamo-cortical tracts that allowed investigating the properties of streamlines in terms of anatomical and functional areas. In order to highlight the extent of the whole cerebello-thalamo-cortical pathway, Figure 1 shows serial sections of the mean pathway seeded in the left SCP across all subjects in MNI space. The greatest density of tracts in the cerebellum is seen in the lateral Crus I-II region (green) and the lateral lobules VIIb/VIII (violet) while in the cerebrum the greatest density of streamlines reaches the prefrontal (yellow), frontal (purple) and temporal (violet) cortices. By comparing *T%gm* values between cerebellar and cerebral cortices in functionally corresponding areas (Table 1), we found that the cerebellar hemispheres and the cortical associative areas received 79% ± 4% and 80% ± 8% of streamlines while the prefrontal cortex and lateral Crus I-II received 38% ± 11% and 48% ± 4% of streamlines, respectively.

Discussion and conclusions: This work shows a characterisation of the cerebello-cortical pathway in terms of functional and anatomical areas touched by streamlines obtained with advanced CSD and TDI techniques. Almost 80% of the streamlines (*T%gm*) reached the cerebellar hemispheres on one side and the associative cerebral cortex on the other, suggesting a prominent connectivity between these areas [7]. This congruent *T%gm* in functionally corresponding areas supports also the coevolution of the two structures [8]. Although tractography is unable to distinguish between single neuron pathways passing though synaptic connections (like the thalamic relay in the cerebello-cortical pathway), it is currently the only *in vivo* in human method for investigating structural connectivity of specific systems. Moreover, given that our analysis was successful using HARDI data acquired on a standard clinical scanner, this method has immediate potential in neurological conditions for which a cerebellar origin has been proposed.

Acknowledgments: *MS Society of Great Britain and Northern Ireland; UCLH/UCL Comprehensive Biomedical Research Centre; Neurological Institute "C. Mondino" of Pavia and University of Pavia for funding.*

References*: 1. Strick PL et al. Annu Rev Neurosci 2009; 32:413-434; 2. Tournier JD et al. Int J Imaging Syst Technol 2012; 22(1):53-66; 3. Cook PA et al. J Magn Reson Imaging 2007; 25(5):1051-8; 4. FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/; 5. Palesi F et al. Proc Int Soc Magn Reson Med 2013; p.3163; 6. Klein A et al. NeuroImage 2009; 46:786–802; 7. Buckner RL et al. J Neurophysiol 2011; 106:2322–2345; 8. Sultan F. Nature. 2002; 415:133–134.*