Contralateral cortico-ponto-cerebellar pathways with prominent involvement of associative areas in humans in vivo

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Target Audience: Researchers and clinicians with an interest in brain structure and function.

Purpose: The cerebellar involvement in both cognition and motor function is increasingly recognised. This is thought to occur through the cerebello-cortical loop, composed of two main pathways: an efferent cerebello-thalamo-cortical (CTC) pathway and an afferent cortico-ponto-cerebellar (CPC) pathway. CTC starts from the cerebellum and reaches the contralateral cerebral cortex passing through the superior cerebellar peduncle and via synapses in the contralateral thalamus, while CPC runs from the cortex through the cerebral peduncles and reaches the contralateral cerebellum via a synaptic link in the pontine nuclei[1]. The anatomical basis of these connections has been established using virus retrograde transport techniques in animals ex vivo[2,3]. Recently CTC has been reconstructed and quantitatively described *in vivo*[4] by combining constrained spherical deconvolution (CSD) with probabilistic tractography[5]. In this study we applied the same method to reconstruct the CPC with the aim of verifying whether *(1)* the CPC pathway can be properly identified as passing through the middle cerebellar peduncle, the pontine nuclei and the cerebral peduncle; *(2)* there is a correspondence between analogous cerebrum and cerebellar's cognitive area.

Methods: MRI acquisition: High Angular Resolution Diffusion Imaging (HARDI) scans were conducted 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 employing 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[6].

Diffusion analysis: HARDI data were analysed using FSL[7] and MRtrix[5] with a defined processing pipeline[4]. Whole brain tractography was performed with MRtrix by using an algorithm combining the CSD technique with probabilistic tractography (seed=whole brain, step-size=0.1 mm, maximum harmonics order=8, 2500000 streamlines) in order to create a track density imaging[8] (TDI) map with a 1 mm resolution by counting the total number of streamlines passing within each element of the grid. Both left and right CPC pathways were reconstructed by tracking the streamlines passing through two regions of interest (ROIs), drawn on the TDI map: the MCP and the whole contralateral cerebral peduncle for each hemisphere[9]. To assess the consistency of the pathways, each subject's pathway was binarized and normalized to the MNI-152 template by using a non-linear transformation algorithm (FNIRT[7]); they were then summed and a threshold (10% of subjects) was applied. To assess the involvement of different cortical regions, cerebral and cerebellar cortices were parcellated based on both anatomy and function, by referring to Brodmann and SUIT atlases (previously aligned to each subject's native space by inverting the normalization transformation). The $trGM_{cROI}$ index[4], obtained dividing grey matter tract volume in one cortical parcellation by grey matter tract volume in all cortical parcellations, was used to assess the percentage by volume of each cortical parcellation involved in the tract.

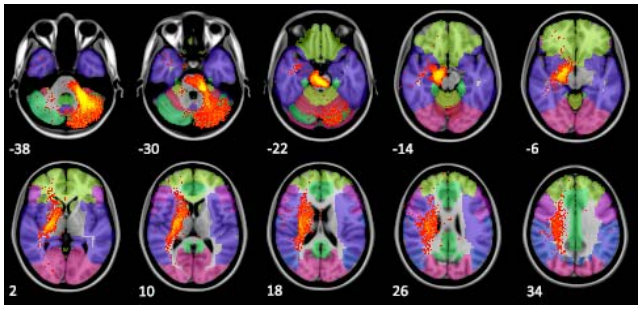

Figure 1: *Left cortico-ponto-cerebellar tract (red-yellow), summed and thresholded, in MNI space. Z coordinate are reported for each slice (mm). Note fiber density in prefrontal cortex and in Crus I-II.*

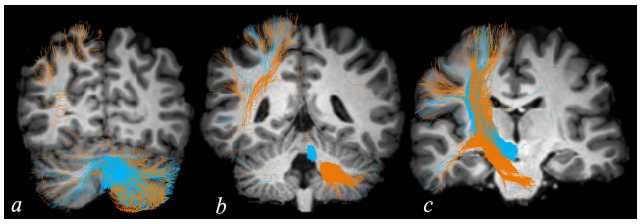

Figure 2: *Left cortico-ponto-cerebellar tract (orange) and cerebello-thalamo-cortical tract (blue). Note that starting and ending areas are partially overlapped (a, c), while outputs from the cerebellum (b) are different.*

	Anatomical Areas	$trGM_{cROI}$ %	Functional Areas	$trGM_{cROI}$ %
Cerebrum	Prefrontal Cortex	8(5)	Motor Area	19(6)
	Frontal Lobe	20(6)	Associative Areas	**69(7)**
	Parietal Lobe	9(4)	Primary Somato-sensory	4(2)
	Temporal Lobe	**54(6)**	Primary Visual Area	6(2)
	Occipital Lobe	6(2)	Primary Auditory Area	2(1)
	Limbic Lobe	3(1)		
Cerebellum	Anter Lobule (I-V)	2(1)	Primary Motor Area	2(1)
	Lobule VI	11(3)	Cognitive/Sensory Area	**96(1)**
	Lateral Crus I-II	**62(4)**	Sensory-Motor Area	2(1)
	Lobules VIIb/VIII	24(5)		
	Infer Lobule (IX-X)	1(0)		

Table 1*: $trGM_{cROI}$ percentage in anatomical and functional areas, each value is averaged over left and right tract. Data are expressed as mean (SD) for each area. Note Associative and Cognitive Areas are the ones with highest value.*

Results: Controlateral CPC pathways were successfully reconstructed by the combined use of CSD and probabilistic tractography, allowing investigation of their properties in terms of $trGM_{cROI}$ both for anatomically and functionally defined areas. In order to highlight the extent of the whole CPC pathway, Figure 1 shows serial sections of the mean pathway across all subjects in MNI space and seeded in the left MCP. From an anatomical point of view, Table1 shows that the majority of CPC streamlines (54% ± 6%) begin in the temporal lobe, and that in the cerebellum CrusI-II receives more streamlines than other areas (62 ± 4%). When looking at functionally-defined parcellations of the brain, the highest $trGM_{cROI}$ is observed in the associative/cognitive areas of both cerebrum and cerebellum.

Discussion and conclusions: In this work the cortico-ponto-cerebellar pathway is described in terms of both anatomically and functionally defined areas reached by streamlines. Most of the CPC streamlines connect cerebral associative areas with their cerebellar cognitive counterpart. This provides a plausible pathway through which the cerebellum can influence cognition and supports the existence of a cerebro-cerebellar closed loop involving both CTC and CPC (Figure 2). As can be seen from a comparison of $trGM_{cROI}$ index in functional areas[4], both CTC and CPC tracts are strongly involved in cognitive ones. In contrast, the proportion of CTC and CPC streamlines reaching the anatomical areas is not a one-to-one relationship. Whereas CTC streamlines occur in the prefrontal cortex more than in other areas, CPC streamlines mostly involve the temporal lobe. Further quantitative investigations are needed to assess the intracortical connection between prefrontal and temporal cortices. Functional and structural MRI studies *in vivo* could help to explain whether the discrepancy between the $trGM_{cROI}$ index in the temporal lobe and prefrontal cortex is a result of inherent limitations of tractography or whether it is anatomically plausible.

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