EVENT ABSTRACT

Characterization of cerebro-cerebellar structural connections using high-quality diffusion MRI data

Fulvia Palesi[1, 2*], Fernando Calamante[3], Giovanni Savini[2, 4], Gloria Castellazzi[2, 5], Egidio U. D'Angelo[2, 6] and Claudia A. Gandini Wheeler-Kingshott[6, 7, 8]

[1] Department of Physics, University of Pavia, Italy
[2] Brain Connectivity Center, C. Mondino National Neurological Institute, Italy
[3] Florey Institute of Neuroscience and Mental Health, University of Melbourne, Australia
[4] Department of Physics, University of Milan, Italy
[5] Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Italy
[6] Department of Brain and Behavioral Sciences, University of Pavia, Italy
[7] Department of Neuroinflammation, UCL Institute of Neurology, United Kingdom
[8] Brain MRI 3T Mondino Research Center, C.Mondino National Neurological Institute, Italy

Introduction

The identification of pathways connecting the cerebral cortex with subcortical structures is critical to understand how large-scale brain networks operate. Among these, the cerebellum is known to project axonal bundles to the cerebral cortex and its involvement in both cognitive and motor functions is increasingly recognized(1). Studies using virus retrograde transport techniques in animals ex vivo have suggested that cerebellar processing is mediated by the cerebro-cerebellar loop, which is thought to be composed of two main pathways: the cerebello-thalamo-cortical (CTC) and, on the returning, the cortico-ponto-cerebellar (CPC) pathway(2). Evidence in humans in vivo of this loop is limited due to technical challenges of reconstructing long polysynaptic tracts. Some recent studies have partially overcome this issue using advanced MRI techniques, such as constrained spherical deconvolution (CSD) algorithm and probabilistic tractography(3-5), assessing the feasibility of reconstructing and characterizing such tracts. In previous studies on healthy subjects we have reconstructed CTC and CPC pathways supporting the hypothesis that the cerebellum has an important role in cognitive functions and suggesting that the cerebro-cerebellar loop relies upon direct connections between cerebrum and cerebellum but also on cerebral intra-cortical connections(5).
In this work CTC and CPC pathways were reconstructed using improved methods in a more automatic approach on high-quality data from the Human Connectome Project (HCP) aiming at confirming and hence extending previous findings.

Methods

Subjects

The study was carried out on 15 subjects (6/9 male/female; 22-35 years) acquired using a Siemens 3T Connectome Skyra scanner. Minimal pre-processed 3DT1-weighted images (0.7mm isotropic resolution resampled at 1.25mm isotropic resolution) and high-quality diffusion weighted data (1.25mm isotropic resolution, b=1000,2000,3000s/mm2, 90 isotropically distributed directions for each shell and 18 images without diffusion weight) were downloaded from the ConnectomeDB (http://db.humanconnectome.org)(6).

Preprocessing

Fractional anisotropy and mean diffusivity maps were created from HCP diffusion data (FSL, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki)(7). Segmentation of white matter (WM), gray matter

(GM), subcortical GM, and cerebrospinal fluid was performed on 3DT1-weighted images (FSL) for using as inputs in the Anatomically-Constrained Tractography (ACT) framework(8).

Whole brain tractography

To account for partial volume effects, fibre orientation distributions (FODs) were calculated separately for each segmented tissue using the multi-shell multi-tissue CSD (MSMT-CSD) technique(9), developed in MRtrix3 (http://www.mrtrix.org/).

Whole-brain tractography was performed using probabilistic streamline tractography (iFOD2) (10) with the following parameters: step size=0.625mm, max angle=45° per step, FOD threshold=0.1, 10 million streamlines selected. The WM-GM interface was used for randomly seeding the streamlines within the ACT framework. To obtain a more biological meaningful marker of axonal fibre count as a measure of structural connectivity, the "Spherical-deconvolution Informed Filtering of Tractograms" (SIFT2)(11) method was used to modulate the contribution weight of each streamline.

Selection of cerebro-cerebellar connections

An ad-hoc atlas was created in MNI152 space combining deep GM structures, Automated Anatomical Labeling(12) and SUIT atlases(13). The atlas comprising a totality of 133 labels was dilated to overlap GM-WM interface and was transformed to subject-space by inverting the non-affine registration from diffusion to MNI space. To select cerebro-cerebellar connections only streamlines connecting cerebral cortical and subcortical structures with contralateral cerebellar cortical areas were considered in the subsequent steps. In order to minimize spurious streamlines, only connections belonging to at least 60% of subjects were taken into account.

Identification of efferent and afferent cerebellar connections

Connections selected in the previous step comprised all streamlines connecting cerebellar and cerebral cortices meaning that streamlines passing through either superior (SCP) or middle cerebellar peduncle (MCP) were considered. SCP and MCP masks were created using a cerebellar white matter atlas(14). To separate efferent, i.e. CTC, and afferent, i.e. CPC, connections to the cerebellum, the SCP and MCP masks were used as follows: i) right and left CTC pathways were identified selecting streamlines passing through the SCP mask and avoiding streamlines passing through the contralateral MCP mask; ii) right and left CPC pathways were identified selecting streamlines passing through the MCP mask and avoiding streamlines passing through the contralateral MCP mask.

Connectivity matrices creation

Streamlines belonging to CTC and CPC pathways connected several cerebellar and cerebral areas to one another. In order to characterize these pathways connectivity matrices were created using streamlines as edges (SIFT2–weighted) and cortical/subcortical regions as nodes.

Results

Figure 1 shows CTC and CPC pathways in terms of cerebral and cerebellar areas directly involved in the connections. Pathways involving left cerebellar structures and right cerebral structures are represented in red while the contralateral pathways are represented in light blue. Here is shown how the CTC pathways mainly reached anterior and medial brain regions, such as prefrontal, frontal and parietal cortices, whereas the CPC pathways reached also posterior and more lateral regions, such as temporal and occipital cortices.

Figure 2 shows connectivity matrices of the CTC and CPC pathways revealing that CPC pathways connect the cerebellum with a higher number of cerebral regions and, moreover, that weights of CPC connections are generally higher with respect to those of CTC connections.

Discussion

Our main finding is that cerebro-cerebellar connections interact with several cerebral structures supporting the increasing role assigned to the cerebellum both in motor functions and in high-cognitive level processes. Indeed, our results demonstrate that both CTC and CPC pathways connect the cerebellum with the frontal cortex (mainly involved in motor functions) but also with parietal and temporal cortices (commonly involved in sensory and cognitive processes). Our findings gave a confirmation and an extension in humans in vivo of results previously discussed by De Rinaldis et al.(5) supporting the fact that cerebro-cerebellar connections could operate in a closed loop if considering also interactions with other intra-cortical cerebral connections. This idea should be further investigated and discussed in future studies aiming at assessing not only cerebro-cerebellar connectivity but also short-range connectivity involving cerebral cortices.

The importance of this work relies also in the fact that state-of-the-art techniques, such as the MSMT-CSD algorithm, together with ACT and SIFT2 techniques, applied to data with the highest possible quality to date at 3T. Nevertheless, further studies are warranted in order to give a quantitative characterization of the tracts involved in the cerebro-cerebellar loop and infer more information regarding cerebellar functions.

Figure 1

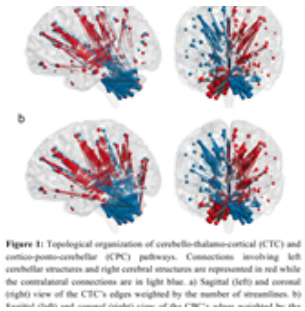
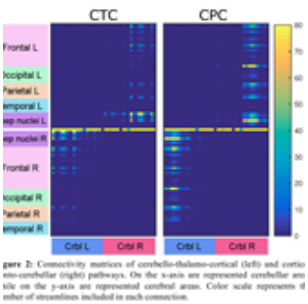


Figure 1: Topological organization of cerebello-thalamo-cortical (CTC) and cortico-ponto-cerebellar (CPC) pathways. Connections involving left cerebellar structures and right cerebral structures are represented in red while the contralateral connections are in light blue. a) Sagittal (left) and coronal (right) view of the CTC's edges weighted by the number of streamlines. b)

Figure 2



gure 2: Connectivity matrices of cerebello-thalamo-cortical (left) and cortico-cerebellar (right) pathways. On the x-axis are represented cerebellar areas while on the y-axis are represented cerebral areas. Color scale represents the number of streamlines included in each connection.

Acknowledgements

Data were provided by Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience, Washington University.

University of Pavia, C. Mondino National Neurological institute (Pavia, IT) for funding (5x1000, year 2013); UCL-UCLH Biomedical Research Centre (London, UK) for ongoing support.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. D'Angelo E, Casali S. Seeking a unified framework for cerebellar function and dysfunction: from circuit operations to cognition. Front Neural Circuits (2013) 6(116):1-23. doi: 10.3389/fncir.2012.00116.
2. Ramnani N. The primate cortico-cerebellar system: anatomy and function. Nat Rev Neurosci (2006) 7(7):511-22. doi: 10.1038/nrn1953.
3. Palesi F, Tournier J-D, Calamante F, Muhlert N, Castellazzi G, Chard D, et al. Contralateral cerebello-thalamo-cortical pathways with prominent involvement of associative areas in humans in vivo. Brain Struct Funct (2015) 220(6):3369-84. doi: 10.1007/s00429-014-0861-2.
4. Kwon HG, Hong JH, Hong CP, Lee DH, Ahn SH, Jang SH. Dentatorubrothalamic tract in human brain: diffusion tensor tractography study. Neuroradiology (2011) 53(10):787-91. doi: 10.1007/s00234-011-0878-7.
5. De Rinaldis A, Palesi F, Castellazzi G, Calamante F, Muhlert N, Tournier JD, et al. Contralateral cortico-ponto-cerebellar pathways with prominent involvement of associative areas in humans in vivo. Proc Int Soc Magn Reson Med (2015) 23:723-.
6. Van Essen DC, Smith SM, Barch DM, Behrens TEJ, Yacoub E, Ugurbil K. The WU-Minn Human Connectome Project: An overview. NeuroImage (2013) 80:62-79. doi: 10.1016/j.neuroimage.2013.05.041.
7. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage (2004) 23(SUPPL. 1):208-19. doi: 10.1016/j.neuroimage.2004.07.051.
8. Smith RE, Tournier J-D, Calamante F, Connelly A. Anatomically-constrained tractography: improved diffusion MRI streamlines tractography through effective use of anatomical information. NeuroImage (2012) 62(3):1924-38. doi: 10.1016/j.neuroimage.2012.06.005.
9. Jeurissen B, Tournier JD, Dhollander T, Connelly A, Sijbers J. Multi-tissue constrained spherical deconvolution for improved analysis of multi-shell diffusion MRI data. NeuroImage (2014) 103:411-26. doi: 10.1016/j.neuroimage.2014.07.061.
10. Tournier J-D, Calamante F, Connelly A, editors. Improved probabilistic streamlines tractography by 2 nd order integration over fibre orientation distributions. 2010 2010; (2010).
11. Smith RE, Tournier J-D, Calamante F, Connelly A. SIFT2: Enabling dense quantitative assessment of brain white matter connectivity using streamlines tractography. NeuroImage (2015) 119:338-51. doi: 10.1016/j.neuroimage.2015.06.092.
12. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage (2002) 15(1):273-89. doi: 10.1006/nimg.2001.0978.
13. Diedrichsen J, Balsters JH, Flavell J, Cussans E, Ramnani N. A probabilistic MR atlas of the

human cerebellum. NeuroImage (2009) 46(1):39-46. doi: 10.1016/j.neuroimage.2009.01.045.
14. Van Baarsen KM, Kleinnijenhuis M, Jbabdi S, Sotiropoulos SN, Grotenhuis JA, Walsum AMVCV. A probabilistic atlas of the cerebellar white matter. NeuroImage (2016) 124:724-32. doi: 10.1016/j.neuroimage.2015.09.014.

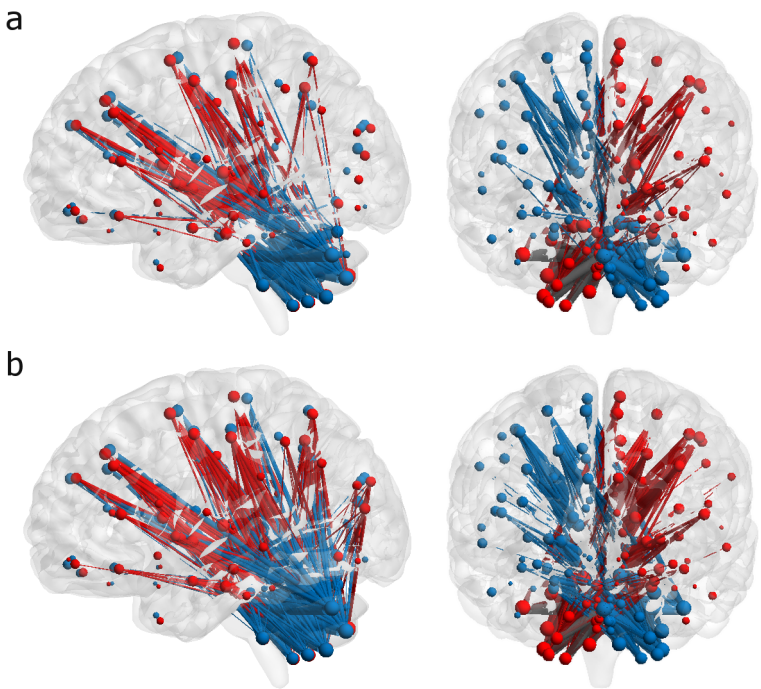
Keywords: cerebro-cerebellar loop, cognitive functions, high-quality DWI, constrained spherical deconvolution, anatomically-constrained tractography

Conference: The Cerebellum inside out: cells, circuits and functions . ERICE (Trapani), Italy, 1 Dec - 5 Dec, 2016.

Presentation Type: poster **Topic:** Integrative nuroscience and MRI

Citation: Palesi F, Calamante F, Savini G, Castellazzi G, D'Angelo EU and Gandini Wheeler-Kingshott CA. Characterization of cerebro-cerebellar structural connections using high-quality diffusion MRI data. *Conference Abstract: The Cerebellum inside out: cells, circuits and functions* .

* **Correspondence:** Dr. Fulvia Palesi, Department of Physics, University of Pavia, Pavia, Italy, fulvia.palesi@unipv.it



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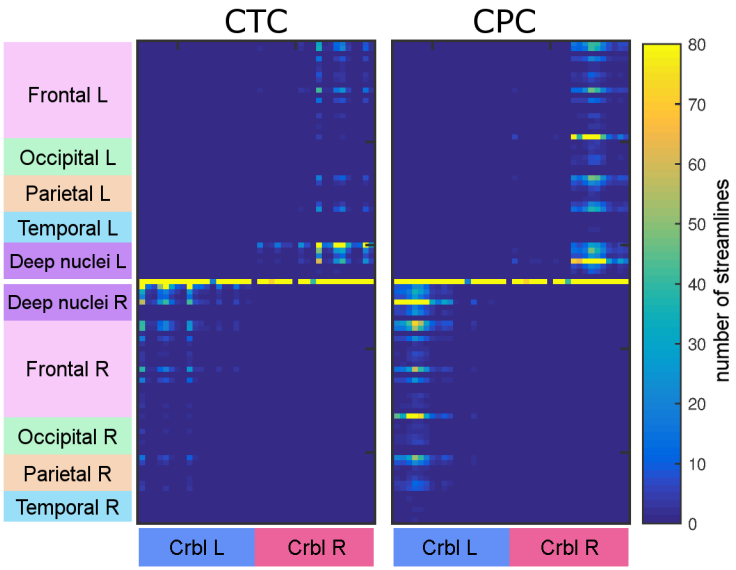

Figure 2: Connectivity matrices of cerebello-thalamo-cortical (left) and cortico-ponto-cerebellar (right) pathways. On the x-axis are represented cerebellar areas while on the y-axis are represented cerebral areas. Color scale represents the number of streamlines included in each connection.