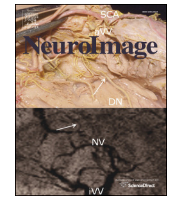
NeuroImage xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg



Full Length Article

A probabilistic atlas of the cerebellar white matter

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ARTICLE INFO

Article history:
Received 21 June 2015
Accepted 7 September 2015
Available online xxxx

Keywords:
Cerebellum
White matter
Atlas
Parcellation map
Probabilistic tractography
Human Connectome Project

ABSTRACT

Imaging of the cerebellar cortex, deep cerebellar nuclei and their connectivity are gaining attraction, due to the important role the cerebellum plays in cognition and motor control. Atlases of the cerebellar cortex and nuclei are used to locate regions of interest in clinical and neuroscience studies. However, the white matter that connects these relay stations is of at least similar functional importance. Damage to these cerebellar white matter tracts may lead to serious language, cognitive and emotional disturbances, although the pathophysiological mechanism behind it is still debated. Differences in white matter integrity between patients and controls might shed light on structure–function correlations. A probabilistic parcellation atlas of the cerebellar white matter would help these studies by facilitating automatic segmentation of the cerebellar peduncles, the localization of lesions and the comparison of white matter integrity between patients and controls.

In this work a digital three-dimensional probabilistic atlas of the cerebellar white matter is presented, based on high quality 3 T, 1.25 mm resolution diffusion MRI data from 90 subjects participating in the Human Connectome Project. The white matter tracts were estimated using probabilistic tractography. Results over 90 subjects were symmetrical and trajectories of superior, middle and inferior cerebellar peduncles resembled the anatomy as known from anatomical studies.

This atlas will contribute to a better understanding of cerebellar white matter architecture. It may eventually aid in defining structure–function correlations in patients with cerebellar disorders.

Introduction

Atlases of the cerebellar cortex and cerebellar nuclei are of great value, but they are not sufficient to map cerebellar anatomy. The white matter that connects these relay stations in the cerebro-cerebellar circuitry is also vital to function. In order to determine white matter structure–function relationships, dedicated cerebellar white matter atlases are needed.

Structural and functional imaging studies of the cerebellar cortex and deep cerebellar nuclei, as well as cerebellar connectivity studies are gaining attraction due to the important but previously underestimated role of the cerebellum in non-motor function (De Smet et al., 2013; Marien et al., 2014; Stoodley, 2012; Stoodley and Schmahmann, 2009; Strick et al., 2009). In fact, damage to the cerebellar white matter has been associated with many cognitive, language and emotional disorders, i.e. in spinocerebellar degeneration, autism spectrum disorder and cerebellar mutism (Becker and Stoodley, 2013; Kawai et al., 2009; Kuper and Timmann, 2013). However, the exact pathogenesis is still under discussion. On the one hand, cerebellar cortical areas seem to be directly involved in language and cognitive functions (Stoodley and Schmahmann, 2009). White matter lesions may disconnect these areas. On the other hand, cerebellar white matter lesions might lead to a hypoactivity in supratentorial areas of the brain by disruption of the cerebello-cerebral circuitry, resulting in language and cognitive dysfunction (Catsman-Berrevoets and Aarsen, 2010; van Baarsen and Grotenhuis, 2014). The relationship between type and location of the white matter lesion, supra- or infratentorial cortical hypoactivity and clinical deficits has not been clarified yet.

Abbreviations: DTI, diffusion tensor imaging; DWI, diffusion weighted imaging; FA, fractional anisotropy; FMRIB, Oxford Centre for Functional MRI of the Brain; FNIRT, FSL non-linear registration tool; FSL, FMRIB Software Library; HCP, Human Connectome Project; ICP, inferior cerebellar peduncle; IIT, Illinois Institute of Technology; JHU, Johns Hopkins University; MCP, middle cerebellar peduncle; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; ROI, region of interest; SCP, superior cerebellar peduncle; SEM, standard error of the mean; SUIT, spatially unbiased infratentorial template.

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http://dx.doi.org/10.1016/j.neuroimage.2015.09.014
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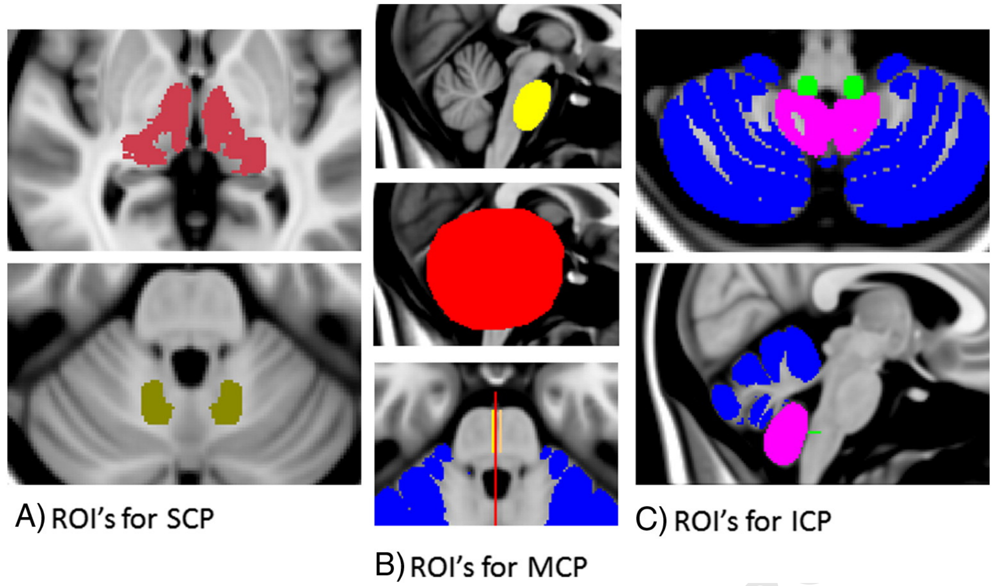

Fig. 1. Regions of interest used for tractography, overlaid on the 1 mm T1-weighted MNI template. A. Regions of interest for estimating the superior cerebellar peduncle (SCP). Top panel: thalamic subnuclei from the Oxford Thalamic Connectivity Atlas (Behrens et al., 2003), pictured in dark red, were used as waypoint and stop masks. Bottom: right and left dentate nuclei depicted in khaki green were used as seed masks. B. Regions of interest for estimating the middle cerebellar peduncle (MCP). The belly of the pons was segmented in the sagittal plane at X = 88 for the right MCP (yellow) and X = 91 for the left MCP (orange), which were used as seed masks. The Probabilistic Atlas of the Cerebellum (Diedrichsen et al., 2011), thresholded at 50%, was chosen as a waypoint and stop mask (blue). An exclusion mask was drawn in the mid-sagittal plane at X = 89 (red) to prevent streamlines from crossing to the contralateral hemisphere. C. Regions of interest for the inferior cerebellar peduncle (ICP). Seed regions in the restiform body (bright green) were placed at Z = 24 based on the 1 mm FA skeleton. Again, the Probabilistic Atlas of the Cerebellum (Diedrichsen et al., 2011), thresholded at 50%, was chosen as waypoint and stop region (blue) and the mid-sagittal exclusion mask was used. A second exclusion mask was located in the tonsils to prevent streamlines from crossing the cerebello-medullary fissure (pink).

To allow optimal analysis and interpretation of cerebellar studies, atlases of the cerebellar cortex and nuclei are used to locate regions of interest. Duvernoy's Atlas provides beautiful anatomical images of brain stem and cerebellum, but the information is two-dimensional and not in standard space (Duvernoy et al., 2009). Schmahmann et al. (1999) provided the first digital three-dimensional atlas of cerebellar lobules and fissures in the stereotaxic space of Talairach and Tournoux (Schmahmann et al., 1999). In 2006, Diedrichsen et al. developed a Spatially Unbiased Infratentorial Template for the cerebellum (SUIT), to overcome problems with anatomical inaccuracy in the cerebellar region with the commonly used MNI template (Diedrichsen, 2006). Based on the 1999 atlas of Schmahmann et al, Diedrichsen et al. also developed a cerebellar cortical parcellation atlas in standard space (MNI as well as their own SUIT template) which is convenient in cerebellar functional MRI studies (Diedrichsen et al., 2009). In 2011, they added a probabilistic atlas of the cerebellar nuclei (Diedrichsen et al., 2011).

Although the above mentioned atlases facilitate segmentation of cerebellar lobules and nuclei, they do not cover the cerebellar white matter. Ideally, researchers would provide detailed information on the exact lobule or peduncle measurements are taken in. However, locating each cerebellar area in every subject is very time-consuming and requires a thorough understanding of cerebellar anatomy. A digital atlas would allow the automatic localization of white matter structures in the cerebellum, resulting in easier and more efficient segmentations.

Further, the atlas would provide a template facilitating between-group analyses in clinical studies. Data from large cohorts of patients with cerebellar disorders and healthy subjects are needed in order to compare the anatomy and integrity of white matter fibers in both

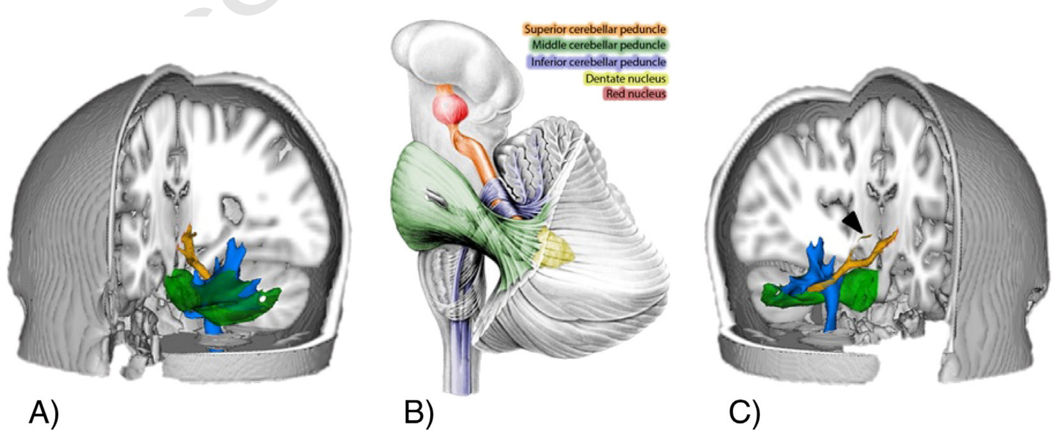

Fig. 2. Correspondence of tractography results with textbook anatomy. A and C: final probabilistic atlases showing the three cerebellar peduncles. A, view from left posterolateral side matches the left-lateral view from panel B, representing the anatomy of the three cerebellar peduncles as it appears in textbooks. With permission from (Nieuwenhuys et al., 2008). C, left cerebellar peduncles from a posteromedial view. Note how the inferior cerebellar peduncle is squeezed between superior and middle ones. Orange: superior cerebellar peduncle; green: middle cerebellar peduncle and blue: inferior cerebellar peduncle. Arrowhead points at the aberrant tract of the left superior cerebellar peduncle. In A, MCP and ICP are made translucent for better visualization, but no thresholds were used.