ORIGINAL ARTICLE

Diffusion tensor imaging (DTI) and tractography of the cerebellar projections to prefrontal and posterior parietal cortices: A study at 3T

Imagerie en tenseur de diffusion et tractographie des voies de projection cérébelleuses vers le cortex préfrontal et pariétal postérieur: étude à 3T

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KEYWORDS
Diffusion tensor imaging;
Tractography;
Cerebellum;
Cerebello-cerebellar circuitry

Abstract
Objective. — Previous diffusion tensor imaging (DTI) studies have identified cerebellar pathways and supratentorial connections, but none of them have isolated cerebellar projections to prefrontal and posterior parietal cortices using tractography. The aim of our study was to identify and visualize on 3D projections, as well as on 2D cross-sectional images, the cerebellar projections to prefrontal (PF) and posterior parietal (PP) cortices.

Material and methods. — The study included 10 healthy volunteers, four males and six females aged 25 to 45 years (mean age 31 years). A DTI sequence was applied at 3 Tesla using diffusion sensitizing gradients in 32 directions. White matter tracts were reconstructed by applying a multiple ROI (region of interest) tractography technique.

Results. — PF projections were obtained in all subjects. PP projections were obtained in six over 10 subjects. On 2D cross-sectional images, the tracts showed the same anatomical location in each ROI in all subjects.

Conclusion. — This DTI study at 3T resulted in a selective and full visualization of cerebellar projections to PF and PP cortices for the first time and is introductive for further optimized and quantitative DTI study of these tracts.

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Introduction

The role of the cerebellum in modulating motor functions of the brain has been established from the early times [1]. During the last years, numbers of studies indicate that cerebrocerebellar interaction is much more complex than previously thought. It has been hypothesized that the cerebrocerebellar circuitry includes non-motor areas of the cerebral cortex and that the cerebellum is an essential node in the distributed cortical–subcortical neural network participating to high cognitive processes [2–5]. This hypothesis has been supported by functional studies in non-human primates and in human, showing corticopontocerebellar projections originating throughout cerebral cortex, in addition to projections from the dentate nucleus of the cerebellum to prefrontal and posterior parietal cortices via the thalamus [6–8]. Diffusion tensor imaging is an advanced magnetic resonance technique that has been used for 2D and 3D representations of white matter tracts [9]. Studies focusing the cerebellum have provided a visualization of afferent and efferent projections within dentate nucleus, the brainstem and the thalamus, on one hand [10] and, on the other hand, the thalamic projections to the cortex [11]. For our knowledge, no diffusion tensor imaging (DTI) study has yet provided a full selective representation of the cerebellar efferent pathways, from the dentate nucleus to prefrontal (PF) and posterior parietal (PP) cortices. We have used the advantages of 3T to detect and visualize these projections.

Material and methods

The study included 10 healthy volunteers, four males and six females, aged 25 to 45 years with a mean age of 31 years. The study received the approval of the ethic committee of our institution and each participant gave a written informed consent. The scans were performed at three-Tesla using a Philips ACHIEVA R1 magnet (Best, The Netherlands) and a SENSE-Head 8 channels coil. The DTI sequence applied was a spin echo EPI single shot (TE: 77 ms, TR: 10,200 ms, FOV 224 x 224 mm, matrix 128 x 128, slice thickness 2 mm, no slice gap, isotropic voxel). Diffusion sensitizing gradients were applied in 32 directions. Two b values were used: 0 and 1000 s/mm². Sixty contiguous transverse slices were acquired to cover the entire brain volume. Acquisition time for each scan was 13 min. Fractional anisotropy (FA) color maps were obtained and tractography performed by using the integrated Philips "advanced tool" R2. White matter tracts were reconstructed by applying a multiple region of interest (ROI) tractography technique. ROI locations were determined on the basis of previous works published in the literature and neuroanatomy atlases [10,12–17]. Seven ROIs (Figs. 1–3), for each tract (prefrontal and posterior parietal), were manually drawn on the fused b0-FA map images and anatomically located as following:

- ROI 1: the entire thalamus at the level of its ventral aspect with attention to the internal capsule–thalamus interface (Fig. 1a);
- ROI 2: surrounding the red nucleus, in a crescent shape, including mostly cerebello-thalamic fibers (Fig. 2a);
- ROI 3: prefrontal paraventricular area (green color on FA map) with attention to prefrontal callosal projections (Fig. 1b);
- ROI 4: anterior and medial prefrontal cortex, including mostly Brodman area 9 (superior frontal gyrus) (Fig. 1b);
- ROI 5: superior cerebellar peduncle (Fig. 2b);
- ROI 6: dentate nucleus at the level of middle cerebellar peduncles (Fig. 3);
- ROI 7: internal posterior parietal cortex leaning on the parieto-occipital fissure and corresponding to Brodman area 7 (Fig. 1c).
Tractography of the prefrontal projections was processed by combining ROIs 1–6 and, posterior parietal projections by combining ROIs 1, 2, 5, 6 and 7. The tracking started for FA greater than 0.10 and stopped for a FA lesser than 0.10 or a deflection angle greater than 45, with minimal length fiber of 10 mm. An eigenvector ($v_1$) associated with the largest eigenvalue ($\lambda_1$) was assumed to represent the local fiber direction. Then, 2D cross-sectional images of tracts were generated on both fused b0-FA and color FA maps images, on axial and coronal planes, as well as 3D projections.
Figure 4  Graph representing PF and PP tracts length (mm) in all subjects, with lack of PP tracts in four of them (2, 4, 6, and 10).
Figure 4  Graphique représentant la longueur des faisceaux PF et PP chez tous les sujets ; le faisceau PP n’est pas visualisé chez quatre sujets (2, 4, 6, et 10).

Figure 5  3D projections of PF and PP tracts; (a): PF in blue and PP in pink project throughout multiple ROIs; (b) PF projection in a subject lacking PP fibers; PF fibers are in directional anisotropy color standard code; (c,d): projections in two different subjects with respectively, fused B0-FA (including ROIs; PF in pink, PP in green) and B0 (without ROIs; PF in blue, PP in pink) background.
Figure 5  Projections 3D des faisceaux PF et PP ; (a) : projections PF en bleu et PP en orange au travers des différentes ROIs ; (b) : projections PF chez un sujet ne montrant pas de faisceau PP avec codage couleur des fibres selon la direction d’anisotropie ; (c,d) : projections des fibres chez deux sujets, respectivement sur fond d’image anatomique résultant de la fusion B0 - carte d’anisotropie (FA) (avec les ROIs, PF en orange et PP en vert) et sur fond de B0 (sans les ROIs, PF en bleu et PP en orange).
Prefrontal projections were obtained in all subjects. Posterior parietal projections were obtained in six over 10 subjects. Table 1 shows mean FA, mean diffusivity (ADC) and fiber length for all subjects. Fig. 4 offers a graph that represents fibers length for each tract in all subjects. On 2D images (Figs. 5–10), the tracts had the same anatomical location in each ROI in all subjects, for prefrontal projections, as well as for posterior parietal projections when visible.

Results

Prefrontal projections were obtained in all subjects. Posterior parietal projections were obtained in six over 10 subjects. Table 1 shows mean FA, mean diffusivity (ADC) and fiber length for all subjects. Fig. 4 offers a graph that represents fibers length for each tract in all subjects. On 2D images (Figs. 5–10), the tracts had the same anatomical location in each ROI in all subjects, for prefrontal projections, as well as for posterior parietal projections when visible.
Table 1  Parameters of the tracts visualized after tractography in all subjects.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>PF tracts</th>
<th>PP tracts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mF A</td>
<td>mADC (10^-3 mm^2/s)</td>
</tr>
<tr>
<td>1</td>
<td>0.458</td>
<td>0.798</td>
</tr>
<tr>
<td>2</td>
<td>0.420</td>
<td>0.744</td>
</tr>
<tr>
<td>3</td>
<td>0.411</td>
<td>0.769</td>
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<tr>
<td>4</td>
<td>0.486</td>
<td>0.750</td>
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<tr>
<td>5</td>
<td>0.454</td>
<td>0.789</td>
</tr>
<tr>
<td>6</td>
<td>0.387</td>
<td>0.821</td>
</tr>
<tr>
<td>7</td>
<td>0.453</td>
<td>0.768</td>
</tr>
<tr>
<td>8</td>
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<td>0.795</td>
</tr>
<tr>
<td>9</td>
<td>0.498</td>
<td>0.719</td>
</tr>
<tr>
<td>10</td>
<td>0.463</td>
<td>0.857</td>
</tr>
</tbody>
</table>

PF, prefrontal; PP, posterior parietal; mF A, mean fractional anisotropy; mADC, mean apparent diffusion coefficient.

Discussion

Our study aimed to detect and visualize the cerebellar efferent pathways, from the dentate nucleus to prefrontal and posterior parietal cortices. For our knowledge, this is the first selective DTI representation of the cerebellar output pathways to the non-motor areas of the cerebral cortex. The selection and precise anatomical location of the ROIs were critical for this study.

The evidence of cerebellar output channels to prefrontal and posterior parietal cortices came up from anatomical and functional studies [18–24]. Middleton and Strick have developed the use of transneuronal transport of herpes simplex virus type 1 in both anterograde and retrograde injections for labelling synaptically linked neurons [6,22–24]. The prefrontal areas 9 and 46 were identified to receive direct output from the dentate nucleus. These areas have been reported to be involved in "working memory" and guidance of behaviour based on transiently stored information [23]. In our study, we focused only the area 9 because of the easiness to identify its anatomical limits that allowed a confident manual drawing of the ROI 3. The studies mentioned above identified the dentate nucleus projections of the prefrontal areas to be located in the ventral and medial portion of the nucleus [22–24]. Clower et al. [20] as well as Dum and Strick [25], using the same virus tracing method respectively in non-human primates and in human, have identified PF (area 9l) and PP (area 7b) projections to be close to each other in the ventral dentate. Our 2D cross-sections at the level of dentate nucleus demonstrate the same location for prefrontal projections (Fig. 6). Moreover, we observed an identical topographic organization within the dentate nucleus, with PF fibers located anteriorly and medially to PP fibers.

Superior cerebellar peduncles (SCP) are well-known to be the pathways of efferent cerebellar fibers from dentate and other deep cerebellar gray nuclei that project to the cortex [10,16,26]. Our 2D cross-sections show, at the SCP level (ROI 5), both PF and PP tracts, with an anterior and lateral disposition for the latter (conversely in comparison...
with dentate nucleus) (Fig. 7). We did not observe the SCP decussation which is known to occur at the level of the midbrain. ROI 5 was located at the level of the presumed decussation or right below. The lack of observing this decussation by tractography is due to the well-known “kissing effect” when two fibers have a crossing trajectory [16].

In a recent DTI study, Habas and Cabanis have described prefrontal and sensorimotor cortical projections to the human red nucleus [27]. Pong et al. mentioned that the red nucleus receives projections from the dentate nucleus in cats [28]. Neuronal labelling studies in human found the prefrontal projections from the cerebellum to run through the rostral part of the substantia nigra (pars reticulata), which is superior, and posteromedial located [22]. In our study, we wanted to avoid the sensorimotor and premotor cortices projections to the red nucleus. We assumed that the cerebello-thalamic connection trajectory in the mesencephalon is located between the red nucleus (medially), the medial lemniscus (laterally), the mesencephalic reticular formation (posteriorly) and the substantia nigra (anteriorly) (Fig. 8) [26]. Our 2D section images show at that level an antero-medial position of PF fibers and a posterolateral location of PP fibers in relation to the red nucleus (Fig. 8).
At the level of ROI 2, around the red nucleus, it is more difficult to define the anatomical projection area. They seem to project to the area encompassing mesencephalic reticular formation as well as spinothalamic tracts.

ROI 1 was drawn over the entire thalamus at the level of its ventral aspect according to all previous studies, identifying the ventral portion of the thalamus as a major relay for the cerebellar PF and PP projections [11,19,22,26]. The thalamus is well-known in having connections with many cortical areas and to be thus involved in motor as well as cognitive tasks [6,16]. A connectivity-based segmentation of the thalamus has been performed by Behrens et al. in a single subject [11]. In this thalamic mapping, the anterior superior and ventrolateral portion is connected with PF cortex, while the posterior and ventrolateral portion is connected with PP cortex. Our 2D cross-sections at that level show the same location of PF and PP fibers (Fig. 9).

In our study, it was somewhat hard to define the exact location of the ROI in order to select uniquely the PF fibers. We wanted to avoid callosal and cortical associative fibers. ROI 3 location was defined after several seeding tests around the frontal periventricular white matter. ROI 4 was designed to cover the entire area 9. But the tractography did not show for PF fibers a continuation to the subcortex, after running the medial part of the anterior limb of the internal capsule (Fig. 9d and Fig. 10a,b). We presumed that PF fibers tractography stops there probably because it’s a "crossroad" point for all frontal fibers. ROI 7 was designed to cover the entire area 7 (called 7b by Dum and Strick [25]). When visible, we could follow PP fibers to the subcortex (Fig. 10c). From the functional point of view, PP is well-known to have a significant participation to visuospatial organization. A recent fMRI study by Swisher et al. have realised a functional mapping of the intraparietal cortex, confirming that PP cortex is involved in various visual tasks like spatial attention, multisensory integration and visuospatial motor planning [29]. Moreover, Danker and Anderson have shown with fMRI procedure the role of PF and PP cortices in high cognitive functions, such as algebra problem solving [30]. The anatomical connection between the cerebellum and PP cortex, observable by tractography, emphasizes the impact of cerebellar output on high cognitive functions.

In our study, PP fibers were visualized only in 60% of case and less obviously than PF fibers. This is likely due to technical limitations. Working at 3T allows increasing the signal to noise ratio and spatial resolution of DTI [9]. However, high magnetic field is more sensitive to susceptibility artefacts and does not overcome some DTI intrinsic limitations, like voxel B0 inhomogeneities and distortion, as well as partial volume effect. A multiple ROI tractography technique was the only one to allow us a selective visualization of fibers running throughout these cerebellar efferent specific pathways, with a lesser susceptibility to partial volume effect and exclusion of branching fibers [16]. We cannot be absolutely confident in naming these tracts "efferent" since DTI does not allow visualizing separately the upward and downward orientation of fibers. Unfortunately, we could not avoid corticopontine fibers projections. Even though, our 2D cross-sectional representation of PF and PP fibers is similar to what can be seen in the fiber tract-based atlas of human white matter anatomy [16].

Figure 10  PF (green) and PP (red) projections on 2D cross sections with B0 background, respectively at the level of frontal periventricular white matter (WM) area (a; ROI 3), prefrontal WM (b; ROI 4) and internal posterior parietal cortex (c; Brodman area 7).

Figure 10  Projections PF en vert et PP en rouge sur les tranches de section 2D sur fond B0, respectivement au niveau de la substance blanche (SB) frontale périventriculaire (a ; ROI 3), de la SB préfrontale (b ; ROI 4) et du cortex pariétal postérieur interne (c ; aire 7 de Brodman).
Conclusion

With this 3T DTI study, we have provided a selective and full visualization of cerebellar projections to PF and PP cortices for the first time. The review of the literature about the cerebellar anatomical and functional connectivity with these brain areas supports the reliability of our observations. We consider these results as preliminary and introductory for a more detailed, optimized and quantitative 3T DTI study to definitely set these anatomical pathways (notably PP fibers) and to assess the human variability of these fibers. Since the involvement of cerebellum in high cognitive functions is more and more recognized, clinical applications will easily arise from such a study, namely mental retardation as well as psychiatric and degenerative disorders.

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References