The nondecussating pathway of the dentatorubrothalamic tract in humans: human connectome-based tractographic study and microdissection validation

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OBJECTIVE The dentatorubrothalamic tract (DRTT) is the major efferent cerebellar pathway arising from the dentate nucleus (DN) and decussating to the contralateral red nucleus (RN) and thalamus. Surprisingly, hemispheric cerebellar output influences bilateral limb movements. In animals, uncrossed projections from the DN to the ipsilateral RN and thalamus may explain this phenomenon. The aim of this study was to clarify the anatomy of the dentatorubrothalamic connections in humans.

METHODS The authors applied advanced deterministic fiber tractography to a template of 488 subjects from the Human Connectome Project (Q1–Q3 release, WU-Minn HCP consortium) and validated the results with microsurgical dissection of cadaveric brains prepared according to Klingler's method.

RESULTS The authors identified the “classic” decussating DRTT and a corresponding nondecussating path (the nondecussating DRTT, nd-DRTT). Within each of these 2 tracts some fibers stop at the level of the RN, forming the dentatorubro tract and the nondecussating dentatorubro tract. The left nd-DRTT encompasses 21.7% of the tracts and 24.9% of the volume of the left superior cerebellar peduncle, and the right nd-DRTT encompasses 20.2% of the tracts and 28.4% of the volume of the right superior cerebellar peduncle.

CONCLUSIONS The connections of the DN with the RN and thalamus are bilateral, not ipsilateral only. This affords a potential anatomical substrate for bilateral limb motor effects originating in a single cerebellar hemisphere under physiological conditions, and for bilateral limb motor impairment in hemispheric cerebellar lesions such as ischemic stroke and hemorrhage, and after resection of hemispheric tumors and arteriovenous malformations. Furthermore, when a lesion is located on the course of the dentatorubrothalamic system, a careful preoperative tractographic analysis of the relationship of the DRTT, nd-DRTT, and the lesion should be performed in order to tailor the surgical approach properly and spare all bundles.

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KEY WORDS dentate nucleus; red nucleus; fiber tractography; thalamus; fiber dissection; fiber tracts; anatomy

THE dentatorubrothalamic tract (DRTT) is the major efferent pathway from the deep cerebellar nuclei to the brainstem and thalamus. Traditionally, its presumed role has been the motor coordination and timing of movement, but increasing evidence suggests an important role in cognitive function such as planning, verbal fluency, working memory, abstract thinking, and behavior.³³ Vari-

ous studies have shown that the DRTT is involved in cerebellar mutism after resection of posterior fossa tumors and hemorrhage,²⁴ schizophrenia,⁵ autism,²³ and bipolar disorder.²⁸

Anatomically, the DRTT is classically described as a bundle arising from the deep cerebellar nuclei, mainly the dentate nucleus (DN), running in the superior cerebellar

ABBREVIATIONS DN = dentate nucleus; DRT = dentatorubro tract; DRTT = dentatorubrothalamic tract; ¹⁸FDG = 18-fluoro-deoxyglucose; fMRI = functional MRI; HCP = Human Connectome Project; HCP-488 = HCP 488-subject template; ICP = inferior cerebellar peduncle; LL = lateral lemniscus; MCP = middle cerebellar peduncle; nd-DRT = nondecussating DRT; nd-DRTT = nondecussating DRTT; RN = red nucleus; ROI = region of interest; rTMS = repetitive transcranial magnetic stimulation; SCP = superior cerebellar peduncle.

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peduncle (SCP), and then completely decussating to the contralateral red nucleus (RN) to ascend to the thalamus and finally to the cortex.²⁶ Because the corticospinal fibers decussate once again, motor deficits related to unilateral hemispheric cerebellar lesions, such as strokes, hemorrhages, and tumors, would be expected to influence only the ipsilateral limbs.^{13,30} Surprisingly, each cerebellar hemisphere clearly influences bilateral limb movements, as demonstrated by human functional magnetic resonance imaging (fMRI) studies,^{12,14,22,25} human transcranial magnetic stimulation (rTMS) studies,^{10,32} and human motor performance studies,^{17,20,34} as well as neurophysiological studies^{19,35,36} and experimental lesioning studies in monkeys.^{4,7} Although the neuroanatomical basis of this phenomenon is not clear,³⁶ uncrossed projections from the DN to the ipsilateral RN and thalamus were demonstrated in monkeys,^{9,40} a finding that provides a simple and elegant explanation of the bilateral motor influence of each cerebellar hemisphere. Still, the existence of a direct, nondecussating DRTT (nd-DRTT) in the monkey brain is not generally accepted, and such a structure has never been demonstrated in humans.

Thus, in an attempt to clarify the anatomy of the dentatorubrothalamic connections in humans we have applied advanced deterministic fiber tractography to a template of 488 subjects from the Human Connectome Project (Q1–Q3 release, WU-Minn HCP consortium) (HCP-488) and validated our results with microsurgical postmortem dissection of human brains.

Methods

The HCP-488

The WU-Minn HCP consortium is an ongoing NIH-funded, institutional review board–approved project led by Washington University, the University of Minnesota, and Oxford University, which aims to define in detail a “map” of human brain connectivity and function. Results of this project will allow analysis and comparison of brain circuits, behavioral features, and genetic tracts within the same subject and between subjects.³⁹ Data accumulated from 500 subjects were released for the first three quarters (Q1–Q3, June 2014), and 488 healthy subjects (289 females, 199 males; average age 29.15 years, SD 3.47 years) underwent diffusion scanning. The diffusion data were acquired in a Siemens 3-T Skyra scanner using a 2D spin-echo single-shot multiband echo planar imaging sequence with a multiband factor of 3 and monopolar gradient pulse.³⁸ The spatial resolution was 1.25 mm isotropic, TR was 5500 msec, and TE was 89 msec. A multishell diffusion scheme was used. The *b* values were 1000, 2000, and 3000 sec/mm². The total number of diffusion sampling directions was 270. The total scanning time was approximately 55 minutes. The diffusion data were reconstructed using q-space diffeomorphic reconstruction,⁴² a method that reconstructs spin-distribution functions in a stereotactic space. The reconstructed data of the 488 subjects were averaged to create a representative template (DSI studio, freely downloadable at: <http://dsi-studio.labsolver.org/download-images>). Whole-brain fiber tracking was conducted using a deterministic fiber-tracking algorithm.⁴³

Fiber Tractography

The DN was easily identified in the axial T2-weighted sequences of the template (Montreal Neurological Institute) as a crescent-shaped, medially concave, hypointense area, immediately lateral to the fourth ventricle, at the level of the middle cerebellar peduncle (MCP). The seeding region was tailored to enclose the DN. Since the DRTT runs completely inside the SCP, a region of interest (ROI) was created to enclose it. The SCP can be identified on sagittal sections as a structure superior and medial to the MCP, with an oblique orientation from the cerebellum to the midbrain. Finally, the RN and thalami were identified to verify the course of the DRTT after fiber tracking. In particular, the RN is seen as a paramedian round hypointense area in the rostral midbrain, just behind the substantia nigra and the cerebral peduncles. After fiber tracking, only the fibers running from the DN to the RN and the thalamus were selected, according to the definition of the DRTT. Each of the resulting bundles was measured by assessing the number of tracts, tract volume, mean quantitative anisotropy, and quantitative anisotropy standard deviation.

Fiber Dissection Technique

Five normal brains obtained at routine autopsy were fixed in 10% formalin aqueous solution for 4 weeks. Then, the specimens were frozen for 2 weeks at –16°C, according to Klingler’s method.³¹ Progressive dissection of the white matter tracts was performed by peeling off the gray matter and isolating the fiber bundles in their glial sheets. We undertook the fiber dissection studies in the Surgical Neuroanatomy Laboratory at the University of Pittsburgh, with the aid of microsurgical instrumentation and a surgical microscope (6–40 magnification; Carl Zeiss, OPMI CS-NC), as previously reported.¹⁶

We removed the cerebral hemispheres, leaving in place the thalami. Then, the tentorial surface of the cerebellar hemispheres was dissected from the cerebello-mesencephalic fissure anteriorly to the horizontal fissure posteriorly. This exposed the inner core of the cerebellar hemisphere. Because the fibers of the MCP wrap around the DN passing above and below it, the nuclei were exposed by removing the paravermian portion of the most superficial fibers of the MCP¹ (Fig. 1).

From the DN, the ascending course of the fibers of the DRTT was clear. The fibers of the inferior cerebellar peduncle (ICP) that crossed above the DRTT and in front of the DN were left in place. The ependyma covering the SCP was removed, exposing the underlying portion of the DRTT. At the level of the midbrain, the fibers of the lateral lemniscus (LL) were found to bridge above the DRTT, with their well-known oblique course from anterior to posterior and from below to above. The mesencephalic portion of the LL was dissected, exposing the lateral surface of the DRTT inside the midbrain.

Then, the lamina quadrigemina was dissected, exposing the upper part of the floor of the fourth ventricle. The overlying ependyma of the floor of the fourth ventricle was removed and the decussation of the DRTT was evident immediately below, due to the typical crossing course of the fibers coming from both sides.

FIG. 1. Photograph showing dissection of the SCP, nd-DRTT, and DRTT before decussation. *Left* side of figure shows the left DN (L-DN) after removal of the most superficial fibers of the MCP. The MCP was sectioned to expose the fibers of the ICP that ascend to the cerebellum between the MCP and SCP and then bend medially above the SCP. The SCP arises from the L-DN and courses below the ICP and medially to the MCP. *Right* side of the figure shows the right DN (R-DN) fully dissected from surrounding structures except for the right DRTT (R-DRTT) and right nd-DRTT (R-nd-DRTT), which ascend together toward the brainstem, medially to the lateral lemniscus, and posteriorly to the cerebral peduncle.

The course of the DRTT was followed until it reached the RN, which is inside the midbrain, inferomedial to the thalamus, inferolateral to the third ventricle, and posterior to the cerebral peduncle.⁴¹

Results

Fiber Tractography

On each side, we found a bundle of fibers arising from the DN, running superiorly and slightly medially inside the SCP. Most of these fibers decussate to reach the contralateral RN and thalamus. Specifically, the most anterior

and ventral fibers of the SCP cross earlier, forming the caudal part of the decussation, while the fibers that are located more posteriorly and dorsally in the SCP decussate more rostrally. This bundle of fibers corresponds to the classical description of the DRTT (Fig. 2 left).

A smaller bundle of fibers, located in the dorsal part of the SCP, does not decussate and remains dorsal to the contralateral decussating fibers, reaching the ipsilateral RN and thalamus. This bundle is the nd-DRTT (Fig. 3 left). As expected, some of the fibers arising from the DN terminate in the RN and some continue to the thalamus.

Thus, within each SCP there are 4 groups of fibers: the “classical” decussating DRTT fibers, or simply the DRTT, which includes a small component of fibers terminating in the RN (dentatorubro tract, DRT); then there is the corresponding nondecussating path, the nd-DRTT, which includes a small component of fibers terminating in the RN (nondecussating dentatorubro tract, nd-DRT) (Fig. 2 left).

The quantitative analysis revealed that globally the left nd-DRTT encompasses 21.7% of the tracts and 24.9% of the volume of the left SCP and the right nd-DRTT encompasses 20.2% of the tracts and 28.4% of the volume of the right SCP (Table 1).

Microsurgical Dissection

From the DN, the ascending course of the fibers of the DRTT was clear (Fig. 1). The fibers of the ICP crossing above the DRTT and in front of the DN were left in place. The ependyma covering the SCP was removed, exposing the underlying portion of the DRTT. At the level of the midbrain, the fibers of the LL were found to bridge above the DRTT, with their well-known oblique course from anterior to posterior and below to above. The mesencephalic portion of the LL was dissected, exposing the lateral surface of the DRTT inside the midbrain.

Then, the lamina quadrigemina was dissected, expos-

FIG. 2. Bilateral dentatorubrothalamic system, depicted by fiber tracking reconstruction (*left*) and dissection (*right*). **Left:** From the left, the fiber bundles are the left nd-DRTT (L-nd-DRTT), containing the left nd-DRT (light pink), and the left DRTT (L-DRTT), containing the left DRT (light green). From the right, the bundles are the right nd-DRTT (R-nd-DRTT), containing the right nd-DRT (light yellow), and the right DRTT (R-DRTT), containing the right DRT (light red). **Right:** The L-nd-DRTT and the R-nd-DRTT ascend dorsally and posteriorly to the R-DRTT and L-DRTT before and after their decussation (Dec.). In each DRTT, the more ventral the fibers are, the more caudally they are located in the decussation. LT = left thalamus; RT = right thalamus.

FIG. 3. Lateral views of the right-ending dentatorubrothalamic system depicted by fiber tracking reconstruction (*left*) and anatomical dissection after removal of right thalamus (RT) and identification of right RN (R-RN) (*right*). **Left:** The left DRTT (L-DRTT) arises from the left DN (L-DN) and decussates to the R-RN and to the RT. The right nd-DRTT (R-nd-DRTT) arises from right DN (R-DN), ascends to R-RN and RT remaining dorsal to L-DRTT after decussation. **Right:** The R-nd-DRTT ascends posteriorly and dorsally to both the R-DRTT before decussation (Dec.) and the L-DRTT after decussation to reach the R-RN posterior to the cerebral peduncle (Cer. ped.), and inferolateral to the third ventricle (3rd Vent.).

ing the upper part of the floor of the fourth ventricle. The overlying ependyma of the floor of the fourth ventricle was removed and the decussation of the DRTT was evident immediately below, due to the typical crossing course of the fibers coming from the two sides.

As expected, most of the DRTT fibers decussate contralaterally to ascend to the RN. In particular, most anterior and ventral fibers of the SCP cross earlier, forming the caudal part of the decussation, and the fibers located more posteriorly and dorsally decussate more rostrally (Fig. 2 right). Surprisingly, a few fibers of the DRTT do not decussate. These are located in the most dorsal part of the DRTT and remain dorsal to the decussated fibers, creating the nd-DRTT (Figs. 2 right and 3 right).

Discussion

A bilateral influence on limb movement by the individual cerebellar hemispheres was clearly shown in several fMRI studies under physiological conditions.^{12,14,22,25} Findings within previous studies that indicated only an ipsilateral influence were attributed to methodological issues, such as insufficient complexity and attentional demand of

motor tasks.¹² Furthermore, rTMS studies in humans indicated a bilateral influence of cerebellar hemispheres. In fact, rTMS consists of the application of a train of pulses transcranially, which induces a temporary “virtual” lesion by suppressing the neural excitability of superficial cortical target regions. rTMS allows study of the clinical effects of a cerebellar hemispheric lesion in vivo. In particular, the application of rTMS to a single cerebellar hemisphere resulted in a bilateral impairment on peg-board motor performance testing.³² By complementing rTMS with 18-fluoro-deoxyglucose positron emission tomography (¹⁸FDG-PET), bilateral cortical cerebral influence after unilateral cortical cerebellar hemispheric depression was confirmed. Furthermore, ¹⁸FDG-PET detected a consensual ipsilateral activation of the DN¹⁰ that is clearly explained by the rTMS-induced depression of GABAergic transmission from Purkinje cells to the DN.²¹ These data suggest that the linkage between the cerebellar hemispheric cortex and the cerebral cortex bilaterally is accomplished by activation of the DN and its efferent pathways.

When a cerebellar hemisphere was involved, whether by pathology (ischemic stroke or hemorrhage) or resection (for tumor or arteriovenous malformation), bilateral limb

TABLE 1. Dentatorubrothalamic system bundles measurements

Bundle	Tracts (no.)	Tracts %	Vol (ml)	Vol %*	Quantitative Anisotropy	
					Mean	SD
Lt SCP	404	100	1489	100	0.65	0.44
Lt DRTT	316	78.3	1118	75.1	0.69	0.47
Lt nd-DRTT	88	21.7	371	24.9	0.82	0.63
Rt SCP	390	100	1457	100	0.82	0.63
Rt DRTT	311	79.8	1043	71.6	0.64	0.41
Rt nd-DRTT	79	20.2	414	28.4	0.69	0.47

* Presented as the percentage of the ipsilateral SCP.

motor impairment was shown.^{17,20,34} Interestingly, the DN was the only common region affected in all examined patients in the study by Fisher et al.,¹⁷ whose findings suggest that the reasons for bilateral impairment could be found in the output fibers arising from the DN, namely the DRTT.

Nonetheless, the neuroanatomical basis by which the cerebellar hemisphere can simultaneously influence bilateral cortical activity and limb motor performance is unclear.

Studies in monkeys,⁹ rats,⁶ and cats,¹⁸ which have demonstrated uncrossed projections from the DN to the ipsilateral RN and thalamus, offer a potential explanation.³⁶ In monkeys, this evidence was confirmed by the injection of a retrograde neuronal marker, horseradish peroxidase, into cortical motor areas 4 and 6.⁴⁰ However, the existence of a direct DRTT in monkeys is not widely accepted and is highly controversial.^{8,11}

Our study shows that the connections of the DN with the RN and the thalamus are bilateral and not only contralateral, as traditionally accepted. Thus, we identified the “classical” decussating DRTT, or simply DRTT, and a corresponding nondecussating path that is the nd-DRTT. Within each of these 2 tracts some fibers terminate at the level of the RN, forming the DRT and the nd-DRT (Fig. 2 left). In particular, the nd-DRTT, although much smaller than the DRTT, constitutes a substantial component of the SCP, contributing about one-quarter of the gross volume of the SCP and about one-fifth of its tracts.

Other cortical and subcortical circuits were investigated to explain the bilateral motor effects of the deep cerebellar nuclei, namely the corpus callosum, the corticospinal tract (CST), the rubrospinal tract, the reticulospinal tract, and the interpositospinal tract, and none of them was found to afford an exhaustive explanation for the bilateral motor effects of each single cerebellar hemisphere.³⁶ In particular, the cortical routes, such as the corpus callosum, the CST, and the DRTT, may explain the bilateral cortical activation by the cerebellar nuclei, as seen in the fMRI and rTMS studies in humans.

The corpus callosum may allow the diffusion of cerebellar output from the contralateral to the ipsilateral cortex, but it would require a detectable delay (2–3 msec) in ipsilateral cortical activation with respect to the contralateral side, corresponding to the transcallosal delay in monkeys.³⁷

It is known that 10% of the fibers of the corticospinal tract do not decussate,²⁷ and this may explain the bilateral motor effects originating from each single cerebellar hemisphere. In any case, electrical stimulation of the motor cortex (M1) elicits only a contralateral and not an ipsilateral response² to the activated cortex, so a functional ipsilateral corticospinal tract cannot be identified.

Thus, the dentatorubrothalamic system is a potential anatomical substrate for bilateral limb motor effects originating from each single cerebellar hemisphere and for bilateral limb motor impairment after ischemic stroke, hemorrhage, or resection of hemispheric lesions. Furthermore, from the functional standpoint, the much more relevant proportion of the decussating fibers with respect to the nondecussating fibers inside the SCP can easily explain why the motor effects of focal diseases within a cerebellar

hemisphere affect the ipsilateral more than the contralateral side.

From the clinical viewpoint, there are 3 major implications of the reported data: First, the occurrence of bilateral neurological signs of cerebellar dysfunction should be carefully evaluated in any case of a focal hemispheric cerebellar lesion. In fact, despite fMRI data, the lack of such neuroanatomical evidence often prevented clinicians from screening patients for contralateral cerebellar signs of any entity.²⁰ Second, a careful preoperative tractographic evaluation of the course, displacement, and disarrangement of the nd-DRTT should be performed when a focal neoplastic, vascular, or hemorrhagic lesion is located on the course of the dentatorubrothalamic pathway, namely the cerebellar hemisphere, the SCP, the midbrain, and the diencephalon. Consequently, traditional operative approaches should be tailored to prevent any damage to the DRTT and the nd-DRTT. Third, the functional significance and outcome after unilateral lesions affecting the DN and/or its efferent pathways should be revisited. As demonstrated in monkeys, ipsilateral limb recovery after an experimental unilateral DN lesioning is much faster than after a bilateral DN lesioning, implying that recovery after induction of a unilateral cerebellar lesion is due to intact contralateral cerebellar circuitry.⁴ Accordingly, the nd-DRTT in humans may substantially contribute to functional recovery after a lesion affecting the contralateral hemisphere.

Further studies are required to ascertain whether the nd-DRTT has a different origin inside the DN or a selective termination in the RN and thalamus with respect to the DRTT. In fact, the functional roles of the DRTT and the nd-DRTT might be different to some extent.

Although the combination of postmortem white matter fiber dissection and tractographic techniques has helped our understanding of the 3D anatomy of white matter tracts to a remarkable degree,^{15,16} both techniques have limitations when each is considered alone or when taken together. In particular, postmortem white matter fiber dissection results are contingent on individual skills and anatomical knowledge, making this technique an excellent method for validation of radiological results. On the other hand, the traditional tractographic modalities (e.g., diffusion tensor imaging) are unable to accurately solve the crossing of fibers (the crossing problem) and to accurately identify the origin and termination of fibers (the termination problem), potentially resulting in artifacts and false tracts.^{3,29} Although the advanced deterministic fiber tractography performed in the present study remarkably improved the results compared with traditional tractographic modalities,¹⁵ it still cannot be considered the gold standard for human brain anatomy studies. A combination of deterministic fiber tractography and microdissection is needed to confirm the findings. Furthermore, the selection of the seeding regions and ROIs is based on current neuroanatomical knowledge, but any difference in their placement can theoretically result in different tracts both quantitatively and qualitatively. In the present study we limited any potential mistakes by having the same investigator place all ROIs using constant anatomical parameters in all subjects. Finally, both anatomical and tractographic

approaches provide morphological details about human brain connections, but they do not allow any conclusion as to their actual functions. Thus, the results need to be critically evaluated in the light of current neurophysiological data obtained in humans and animals and of histological studies in animals. In the present study, the existence of the nd-DRTT is in full agreement with previous anatomical and histological studies in animals^{6,9,18,40} and with radiological¹⁷ and neurophysiological data¹⁰ obtained in humans, suggesting that the DN and its projections constitute the “missing ring” in the interaction between the cerebellar hemisphere and the bilateral cerebral cortex.

Conclusions

Our tractographic study, performed on a template of 488 subjects (HCP-488) and validated by microsurgical brain dissection, shows that the connections of the DN with the RN and thalamus are bilateral and not only contralateral, as traditionally accepted. We identified the “classical” decussating DRTT fibers and an ipsilateral nondecussating path, the nd-DRTT, which accounts for about one-fourth of the volume of the SCP and about one-fifth of its tracts. Within each of those 2 bundles some fibers stop at the level of the RN and form the DRT and the nd-DRT.

These results offer a potential anatomical explanation for bilateral limb motor effects of cerebellar hemispheres under physiological conditions, and for bilateral limb motor impairment by hemispheric ischemic stroke and hemorrhage, and resection of hemispheric tumors and arteriovenous malformations. Furthermore, when a lesion is located on the course of the dentatorubrothalamic system, a careful preoperative tractographic analysis of the relationship of the DRTT, nd-DRTT, and the lesion should be performed, to tailor the surgical approach properly and spare both bundles.

Further studies are required to ascertain the functional role of the nd-DRTT, its detailed origin inside the DN, and its particular termination inside the RN and thalamus.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Fernandez-Miranda, Meola. Acquisition of data: Meola, Sivakanthan. Analysis and interpretation of data: Meola. Drafting the article: Meola. Critically revising the article: Fernandez-Miranda, Yeh. Reviewed submitted version of manuscript: Fernandez-Miranda, Meola. Approved the final version of the manuscript on behalf of all authors: Fernandez-Miranda. Administrative/technical/material support: Comert, Yeh. Study supervision: Fernandez-Miranda.

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