Neuroscience Letters 677 (2018) 1–5

Contents lists available at ScienceDirect

Neuroscience Letters

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

Research article

# Revealing the cerebello-ponto-hypothalamic pathway in the human brain

Arash Kamali[a,*], Niloofar Karbasian[b], Pejman Rabiei[a], Andres Cano[a], Roy F. Riascos[a], Nitin Tandon[c], Octavio Arevalo[a], Laura Ocasio[d], Kyan Younes[e], Mahsa Khayat-khoei[e], Saeedeh Mirbagheri[f], Khader M. Hasan[a]

[a] Department of Diagnostic Radiology, The University of Texas Health Science Center at Houston, Houston, TX, USA
[b] Texas Children's Hospital, Houston, TX, USA
[c] Department of Neurosurgery, The University of Texas Health Science Center at Houston, Houston, TX, USA
[d] Memorial Hermann Hospital, TMC, Houston, TX, USA
[e] Department of Neurology, The University of Texas Health Science Center at Houston, Houston, TX, USA
[f] Department of Diagnostic Radiology, Mount Saini Beth Israel, New York, NY, USA

ARTICLE INFO

*Keywords:*
Cerebellum
Cerebello-hypothalamic
Diffusion tensor imaging
High resolution
Hypothalamus
Limbic
Tractography

ABSTRACT

The cerebellum is shown to be involved in some limbic functions of the human brain such as emotion and affect. The major connection of the cerebellum with the limbic system is known to be through the cerebello-hypothalamic pathways. The consensus is that the projections from the cerebellar nuclei to the limbic system, and particularly the hypothalamus, or from the hypothalamus to the cerebellar nuclei, are through multisynaptic pathways in the bulbar reticular formation. The detailed anatomy of the pathways responsible for mediating these responses, however, is yet to be determined. Diffusion tensor imaging may be helpful in better visualizing the surgical anatomy of the cerebello-ponto-hypothalamic (CPH) pathway. This study aimed to investigate the utility of high-spatial-resolution diffusion tensor tractography for mapping the trajectory of the CPH tract in the human brain. Fifteen healthy adults were studied. We delineated, for the first time, the detailed trajectory of the CPH tract of the human brain in fifteen normal adult subjects using high-spatial-resolution diffusion tensor tractography. We further revealed the close relationship of the CPH tract with the optic tract, temporo-pontine tract, amygdalofugal tract and the fornix in the human brain.

## 1. Introduction

In humans, the cerebellum plays an important role in motor control, motor coordination and motor learning. The cerebellum receives input from sensory systems of the spinal cord and from other parts of the brain and integrates these inputs to tune the fine motor activity and coordinate the movements. The cerebellum may also be involved in some cognitive functions such as attention, language, regulating fear and pleasure responses [1]. The influence of the cerebellum on the vegetative function is also a known concept [2,3]. For instance, modification of autonomic system controlling the blood pressure, respiratory rate, heart rate, bladder tone or GI motility, as well as alteration of behavior such as self-confidence or antisocial behavior is representative of autonomic and affective reactions reported after cerebellar manipulation. [4,5].

Most of the autonomic regulation of the cerebellum is known to be through the hypothalamic nuclei and cerebello-hypothalamic (CH) pathways. Some researchers suggested that CH projections might have a role in immunomodulation [6,7]. Animal experiment studies showed that injection of the glutaminase inhibitor in the cerebellar nuclei in rats or creating cerebellar lesions may lead to decrease in the number of peripheral lymphocyte count [6,8]. Wen et al. indicated that cerebellum might participate in the cardiovascular regulation and osmoregulation via the CH projections [7]. This was further confirmed by another study on rats in 2016 by Li et al. which revealed that electrical stimulation of cerebellar nuclei may elicit an excitatory, inhibitory or biphasic response of ventromedial hypothalamic nucleus of the hypothalamus, which is believed to be involved in feeding behavior, energy balance, and weight control [9]. The consensus is that the projections from cerebellar nuclei to the limbic system, and especially the hypothalamus are through pathways synapsing in the bulbar reticular formation known as the cerebello-ponto-hypothalamic pathway (CPH)

*Abbreviations:* CH, cerebello-hypothalamic; CPH, cerebello-ponto-hypothalamic; DTI, diffusion tensor imaging; DTT, diffusion tensor tractography; EPA, echo planar imaging; FA, fractional anisotropy; FACT, fiber assignment by continuous tracking; FOV, field of view; ROI, region of interest; SNR, signal-to-noise ratio

* Corresponding author at: Department of Diagnostic Radiology, Neuroradiology Section, The University of Texas Health Science Center at Houston, 6431 Fannin St, Houston, TX, 77030, USA.
*E-mail address:* arash.kamali@uth.tmc.edu (A. Kamali).

https://doi.org/10.1016/j.neulet.2018.04.024
Received 2 November 2017; Received in revised form 7 April 2018; Accepted 13 April 2018
Available online 17 April 2018

[10–12]. The human hypothalamus is a collection of small nuclei located in the ventral aspect of the diencephalon which regulates the autonomic nervous system, controls the pituitary function, and receives abundant sensory inputs and interacts with the rest of the limbic system [1].

Poor signal-to-noise ratio (SNR) due to use of small voxel volumes, low spatial resolution and partial volume averaging upon using large voxel volumes have been major restrictions of diffusion tensor tractography (DTT) study of the fine pathways of the limbic system. For example, the trajectory of the CPH tract has not been elucidated before by prior DTT studies.

This work set out to investigate the feasibility of tractography of the trajectory, connectivity, and descriptive anatomy of the CPH tract of the human limbic system using a high-spatial resolution DTI data on 3T.

## 2. Materials and methods

### 2.1. Study subjects

This work was approved by our institutional review board (IRB) and was health insurance portability and accountability act (HIPAA) compliant. Fifteen right-handed healthy adults (3 females and 12 males age range 24–37 years) were included in this study. The exclusion factor for our study group was the knowledge of any prior brain pathology including the traumatic, neoplastic, demyelinating disease, or degenerative diseases based on the history and review of the brain MRI by a neuroradiologist.

### 2.2. Conventional MRI data acquisition

All MRI studies were performed on a 3T Philips Intera scanner with a dual quasar gradient system with a maximum gradient amplitude of 80 mT/m, maximum slew rate 200 mT/ms/m, and an eight-channel SENSE-compatible head coil (Philips Medical Systems, Best, Netherlands). The conventional MRI (cMRI) protocol included axially prescribed 3D spoiled gradient (repetition time, TR = 8 ms; echo time, TE = 4 ms; and flip angle = TR/TE/flip angle = 8 ms/4 ms/6°), 3-D proton density-weighted (TR/TE/flip angle = 10,000 ms/10 ms/90° and 3-D $T_2$-weighted (TR/TE/flip angle = 10,000 ms/60 ms/90°), with a square field-of-view (FOV) = 256 mm × 256 mm and a matrix of 256 × 256 pixels. The slice thickness for the MRI sequences was 1.0 mm with 120 contiguous axial slices covering the entire brain (foramen magnum to vertex).

### 2.3. DTI data acquisition

Diffusion-weighted image (DTI) data were acquired axially from the same graphically prescribed cMRI volumes using a single-shot multislice 2D spin-echo diffusion sensitized and fat-suppressed echo planar imaging (EPI) sequence, with the balanced Icosa21 tensor encoding scheme. The b-factor = 500 s $mm^{-2}$, TR/TE = 14460/60 msec. The spatial coverage for DTI data matched the 3D cMRI spatial coverage (FOV = 256 mm × 256 mm and slice thickness/gap/#slices = 1 mm/0 mm/120). The EPI phase encoding used a SENSE k-space undersampling factor of two, with an effective k-space matrix of 112 × 112 and an image matrix after zero-filling of 256 × 256. The acquisition spatial resolution for DTI data was ~2.29 mm × 2.29 mm × 1 mm, and the nominal resolution after image construction was 1 mm × 1 mm × 1 mm. The number of b-factor ~0 ($b_0$) magnitude image averages was four. The total DTI acquisition time was ~ seven min for the diffusion-weighted acquisition. The DTI acquisition was repeated three times to enhance the SNR. The selection of the b-factor, parallel imaging, repetition and echo times enabled entire brain coverage using single-shot and interleaved EPI.

### 2.4. White matter fiber tracking

After data preparation and quality assessment, compact WM fiber tracking was performed using DTI Studio software (http://cmrm.med.jhmi.edu/). Fiber tracking was based on the fiber assignment by continuous tracking (FACT) algorithm with a fractional anisotropy (FA) threshold of 0.22 and angle threshold of 60°. Reproducibility of the fiber construction in both hemispheres was tested by two experienced raters on all subjects. Two ROIs were applied to obtain each fiber tract and an "AND" operation was performed to include the fibers passing through both ROIs.

## 3. Results

We demonstrate the 3D trajectory of the CPH tract in the human brain. We also present major adjacent fiber tracts including the fornix, temporo-pontine tract, amygdalofugal tract and optic tract as well as the relationship of these tracts with the CPH pathway (Fig. 3). The CPH pathway was identified bilaterally in all subjects. We observed a common pattern of CPH tract among the fifteen subjects bilaterally. We further reveal delicate connection of the cerebellum to the septal nuclei (Fig. 4). We also illustrate the coronal and axial mappings of the CPH tract (Figs. 1–3).

### 3.1. The cerebello-ponto-hypothalamic tract (CPHt)

The CPHt is a projection bundle that connects the cerebellum to the contralateral anterior hypothalamic and septal nuclei. The CPHt originates from the cerebellar hemisphere coursing through the ipsilateral middle cerebellar hemisphere. The CPH tract then enters the pons where it crosses to the contralateral pons through the transverse pontine fibers (Figs. 2e–f, 3c). After crossing to the other side, the CPHt then ascends in the pons into the midbrain where it ascends at the junction of the cerebral peduncle/tegmentum of the midbrain (Figs. 2d, 3b). The CPHt then projects into the posterior aspect of the cerebral peduncle and ascends alongside with the temporopontine tract (Fig. 4e). The CPHt deviates laterally into the medial aspect of the parahippocampal gyrus (Fig. 3b). Within the medial margin of the parahippocampal gyrus, the CPHt changes course and projects ventrally along the superior and lateral aspect of the optic tract (Figs. 3b, 4d) (arrows in Fig. 1g). The CPH then projects more medially in relation to the optic tract distally (Fig. 4d). The CPHt courses ventrally alongside the anterior arms of the fornix (Fig. 4c). Finally, the CPHt terminates in the region of the anterior hypothalamic nuclei (arrow in Fig. 3a) just posterior to the optic chiasm (chiasm is shown by an arrow in Fig. 2a) alongside the caudal fibers of the amygdalofugal tract (Fig. 2a–b, arrowhead in Fig. 4f). Some of the fibers at the distal end of this tract course cranially toward the septal nuclei alongside the cranial fibers of the amygdalofugal tract (arrowhead in Fig. 4f).

## 4. Discussion

To the best of our knowledge, the current study is the first to reconstruct the 3D DTI trajectory of the CPH pathway and present the detailed anatomical parcellations of the CPHt in the human brain. Our tractography results are in line with the known connections of this tract from the atlas of anatomy and prior animal dissection studies [1,10,12–16].

Experimental studies on a variety of mammals revealed direct (monosynaptic) and indirect (polysynaptic) projections from the cerebellar nuclei to the hypothalamus [10,12–15]. These connections appear to be bidirectional or at least in part reciprocal [15,13]. The direct cerebellar contributions to the limbic system are established through the cerebello-hypothalamic (CH) fibers. The CH fibers are known to project from the cerebellum into the midbrain through the superior cerebellar peduncles. These fibers cross the midline at the decussation