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Research paper

Red nucleus connectivity as revealed by constrained spherical deconvolution tractography

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HIGHLIGHTS

- Assessing neural connectivity of the red nucleus in humans.
- The red nucleus showed several cortical and subcortical connections.
- The physiology of red nucleus is discussed.

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ABSTRACT

Previous Diffusion Tensor Imaging studies have demonstrated that the human red nucleus is widely interconnected with sensory-motor and prefrontal cortices.

In this study, we assessed red nucleus connectivity by using a multi-tensor model called non-negative Constrained Spherical Deconvolution (CSD), which is able to resolve more than one fiber orientation per voxel.

Connections of the red nuclei of fifteen volunteers were studied at 3 T using CSD axonal tracking.

We found significant connectivity between RN and the following cortical and subcortical areas: cerebellar cortex, thalamus, paracentral lobule, postcentral gyrus, precentral gyrus, superior frontal gyrus and dentate nucleus.

We confirmed that red nucleus is tightly linked with the cerebral cortex and has dense subcortical connections with thalamus and cerebellar cortex. These findings may be useful in a clinical context considering that RN is involved in motor control and it is known to have potential to compensate for injury of the corticospinal tract.

1. Introduction

The red nucleus (RN) is a center of motor integration, involved in the regulation of upper limb movements. It is placed in the rostral midbrain below the aqueduct of Sylvius and borders laterally with the reticular formation and ventrally with the substantia nigra (SN). The RN mainly connects the motor areas of the cerebral cortex to the cerebellum and the spinal cord, through the cortico-rubral (CRT) and rubro-spinal tracts (RST), contributing to voluntary movements. Several studies suggested that the RN may be involved both in posture, since it is able to modulate the activity of α and γ motor neurons [1] and grasping movements coupled with reaching [2,3]

Although its major role in motor function, to the best of our knowledge, only a few Diffusion Tensor Imaging (DTI) studies have investigated the RN connections in the human brain both in normal and pathological conditions [4–7].

DTI is a magnetic resonance imaging technique that allows to evaluate the process of water molecules diffusion within the white matter and to infer the organization of neural fibers estimating the degree of anisotropy. However, it suffers from several limitations, such as partial volume effects and the inability to provide resolution of multiple fiber populations per single voxel [8].

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In the current study, we attempted to overcome DTI limitations and to assess RN connectivity by using a multi-tensor model called non-negative Constrained Spherical Deconvolution (CSD) which is able to resolve more than one fiber orientation per voxel [9–11]. Such powerful technique has been successfully adopted both in physiological and pathological conditions [10–14].

As far as we know, this is the first CSD tractographic study investigating the neural connectivity of the RN in the human brain.

2. Material and methods

2.1. Subjects

We recruited 15 healthy subjects (males: 9, females: 6, mean age 29; age range 25–32 years) with no previous history of any overt neurological, physical, or psychiatric illness. The research followed the reccommendations of the Helsinki Declaration; written informed consent was

obtained from all included subjects, after careful description of the entire procedure. The study was approved by the institutional review board of IRCCS Bonino Pulejo, Messina, Italy (Scientific Institute for Research, Hospitalization and Health Care).

2.2. Data acquisition, pre-processing and co-registration

The data were acquired using a 32-channels SENSE head coil on a 3T Achieva Philips scanner, adopting the following sequences:

1. 3D T1 weighted Fast Field Echo (FFE) sequence (TR = 25 ms, TE = 4.6 ms, flip angle = 30°, FOV = 240 × 240 mm^2; reconstruction matrix 240 × 240 voxel; voxel size 1 mm isotropic);
2. 3D T2 weighted Turbo Spin Echo (TSE) sequence (TR = 2500 ms, TE = 380 ms; FOV = 250 × 250 mm^2; reconstruction matrix 312 × 312 voxel; voxel size 0.8 × 0.8 × 0.8 mm);
3. Dual phase encoded pulsed gradient spin echo Diffusion Weighted sequences [15] using 64 gradient diffusion directions chosen following an electrostatic repulsion model [16] (b-value = 1500 s/mm^2; TR = 11884 ms; TE = 54 ms; FOV = 240 × 240 mm^2; resulting in an isotropic 2 mm voxel size with no inter-slice gap).

Pre-processing steps are widely reported in our previous study [14]. Co-registration of T1 and T2images to DWIs were performed using a pipeline outlined by Besson et al. [17].

2.3. Probabilistic CSD tractography

We used a modified High Angular Resolution Diffusion Imaging (HARDI) technique called non-negative CSD which estimates the fiber Orientation Distribution Function (fODF) directly from deconvolution of DW signal corresponding to single fiber response function [9].

As regard tracking parameters, we used a more conservative approach with respect to usual standars [8,18], as outlined in our previous study [14]. fODF estimation and tractography were determined using MRtrix software (http://jdtournier.github.io/mrtrix-0.2/index.html).

We performed, for each subject, probabilistic whole brain tractography by generating ten millions streamlines using dilated WM masks as seed and mask regions.

For visualization purposes, we reconstructed a color-coded map in which red, blue, and green colours indicate the principal streamline directions, according to the traditional nomenclature [19].

The following formula was used to calculate lateralization index for intra- and inter-subjects variability: (N. Right—N. Left)/(N. Right + N. Left), with N = number of streamlines. Statistical significance of the inter-subjects and intra- subjects variability was determined using a 2-tailed t-test; P values <0.05 were considered statistically significant.

2.4. Cortical parcellation and segmentation

Cortical reconstruction and volumetric segmentation were performed on co-registered T1 images with the Freesurfer image analysis suite, which is widely documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Successively, the obtained parcellation and segmentation of each individual were visually inspected and, if needed, manually edited.

RN segmentation was carried out manually by an expert radiologist based on previously co-registered T2 images in the axial plane superimposed on the color coded map [14].

2.5. Connectivity analysis

Connectivity measures were obtained by means of in-house scripts built with MATLAB Software Package (www.mathworks.com), release 2013. Connectivity was defined as the incidence of connection between the RN and each ROI: hippocampus, amygdala, ventral DC, cerebellum. Thalamus, caudate nucleus, putamen, globus pallidus, nucleus accumbens, cingulate cortex, caudal and rostral middle frontal cortex (cMFC and rMFC), cuneus, precuneus, entorhinal cortex, inferior parietal lobule, inferior temporal gyrus (ITG), middle temporal gyrus (MTG), superior temporal gyrus (STG), transverse temporal gyrus, lateral occipital cortex, lingual cortex, pericalcarine cortex, lateral and medial orbitofrontal cortices, parahippocampal cortex, paracentral lobule, precentral and post central gyri, superior frontal gyrus (SFG), superior parietal lobule, supramarginal gyrus, frontal and temporal poles and insula.

3. Results

In all subjects we were able to identify dense cortical and subcortical connections to the RN.

In particular, we found representative connectivity between RN and the following cortical and subcortical areas: cerebellar cortex, thalamus, paracentral lobule, postcentral gyrus, precentral gyrus, superior frontal gyrus and dentate nucleus. We also found sparse although not significant connections ($p > 0.05$) between RN and other cortical areas and subcortical structures, such as caudal middle frontal gyrus, inferior and superior parietal lobules, middle temporal gyrus and lentiform nucleus. We calculated, for each subject, and for each single region, percentages for both left and right connectivity referred to the totality of tracts between these regions and RN. Mean right and left connectivity values with standard deviations are shown in Table 1 and will be analyzed in details below.

3.1. Dentate nucleus

We found that dentate nucleus is connected with both ipsilateral and contralateral RN, as shown in Fig. 1.

In particular, we found 7.59% of total connectivity between left dentate nucleus and ipsilateral RN, whilst 7.11% of total connectivity was reported between the right dentate nucleus and the ipsilateral RN. In addition, we found 1.82% of total connectivity between left dentate nucleus and contralateral RN and 2.04% of total connectivity between right dentate nucleus and contralateral RN. No lateralization was detected ($p > 0.05$). Ipsilateral pathway involving left RN and dentate nucleus showed the following parameters: FA (0.4012 ± 0.0934), MD (0.0008 ± 0.0001), tract length (104.226 ± 2.739 mm). For contralateral connection involving left RN: FA (0.4178 ± 0.1142), MD (0.0007 ± 0.0002),