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Review Articles

History of the Red Nucleus, its Tracts and Species Evolutionary Choice

Enrico Marani

Tiboel Siegenbeekstraat 15, 2313HA Leiden, The Netherlands;

Corresponding author e-mail: enrico.marani@outlook.com

The red nucleus is a constant in the vertebrate brain. A general pattern of its tracts can be discerned, which is differently applied in human's, mammalian's and bird's brains. At the base of the difference is the magnocellular and parvocellular parts. The magnocellular part axons travel to the contralateral spinal cord, while the parvocellular part projects to the ipsilateral inferior olive. This olivary projection, part of the dentate-rubro-olivary pathway, is associated with olivary hypertrophy. In rodents both red nucleus parts can contribute to the rubro-spinal tract and its development is described. The history of the separation of both human tracts is explained. In birds the crossed tract is solely present and magnocellular and parvocellular areas are debated. The spino-rubral connection is described in relation to perturbation of movements. Special scientific advances discussed concern: asymmetry of the red nucleus, ruber and migraine, mutation and olivary hypertrophy, the red nucleus and POU domain and ruber involvement in restless legs syndrome.

Key words: immuno(cyto)chemistry, rubrospinal, rubro-olivary, tegmental tracts

Introduction

Recently two review articles that concern the red nucleus have been published [1,42]. The general tendency of these articles is that our current knowledge of the anatomy of the red nucleus and its functions are underestimated in research. These overviews of red nucleus research are produced with some important topics unaccounted for that mainly are related to its history. This article starts with highlighting some historic points and pays attention to recent discoveries in the light of previous research.

Architectural stamped (neuro)anatomists

The fundamentals of our knowledge of the brain macroscopy have their origin in the baroque period, starting with the contra-reformation after the Council of Trent

(1545–1563), hence around 1600. It ended towards the French revolution (1750/1780). The Rococo style started in France around 1720, but the baroque kept its influence in architecture after 1720. The baroque seventeenth century was an age of high monarchy. Royal absolutism was the governmental system in France, which was taken over from Renaissance Italy. Protection of arts, stimulation of science and of architecture are the main characteristics of this princely atmosphere in Europe. Architecture elaborated into city planning Versailles, construction of Schönbrunn outside Vienna and creating Sans Souci at Potsdam. The start towards it, the baroque period and its slow ending at the end of the eighteen century all contributed to the interest in the other architecture, that of the brain [29].

These ancient, architectural stamped, (neuro)anatomists studied and named the brain structures from their own daily experience: best known is the naming of "mammillary bodies" mirroring the view on the female breasts in a Bavarian "dirndel" (tavern wench) dress. The cerebellar tonsils resemble the inside of the throat with two inflamed tonsils and the colliculus superior and inferior were compared to the buttocks or nates with its hanging testes below it. This naming habit started far earlier. For example, the Latin nautical term "puppi," referring to the stern of a ship, was applied to the cerebellum in the eleventh century [67]. Niels Stensen (1638-1686) already remarked that using these "household" terms for neuroanatomical structures indicates that the user presumably does not know the real meaning of these brain areas [22]. Description of the brain structure through the ages gives: Varolio (1543-1575) in 1573 discerned cerebrum, spinal marrow and cerebellum, Willis (1621-1675), in 1664, adds striate body, optic thalamus and tectum and its full subdivision is not earlier than by Meynert (1833-1892) in 1872 (**Fig. 1**, [58]).

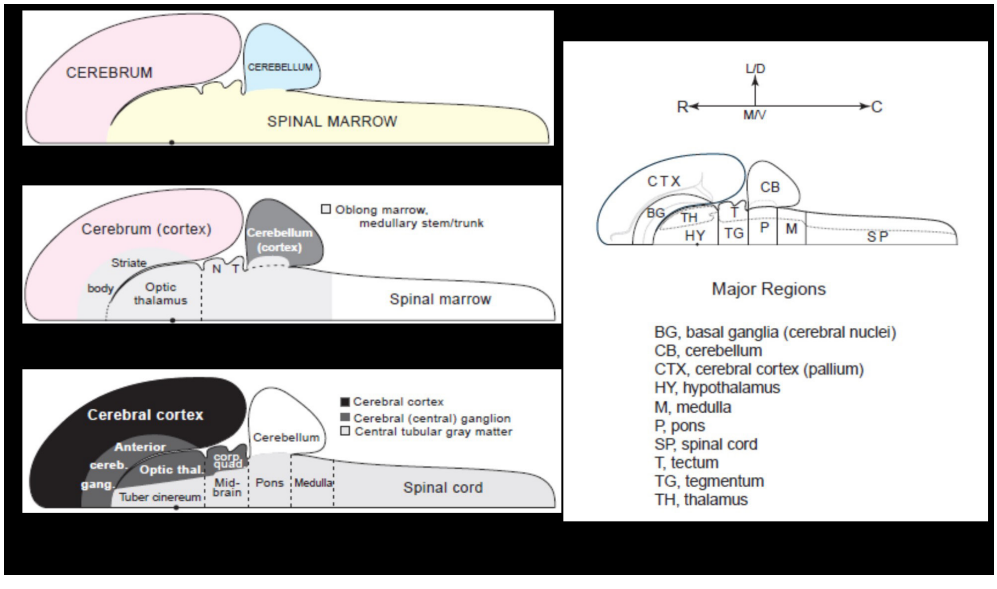


Fig. 1. Segmental subdivision of the brain by Varolio, Willis and Meynert leading to the nowadays accepted brain partition in ten parts ([58]; fig. [33])

Red nuclei and its tracts

The red nucleus is a group of neurons located high in the brainstem, containing small and large neurons that shows a light red glow in non-fixed sections by which it was detected by these early (neuro) anatomists (**Fig. 2**). Note that some scientists name it a small mesencephalic grey matter structure [18], while others termed it a large subcortical structure [1].

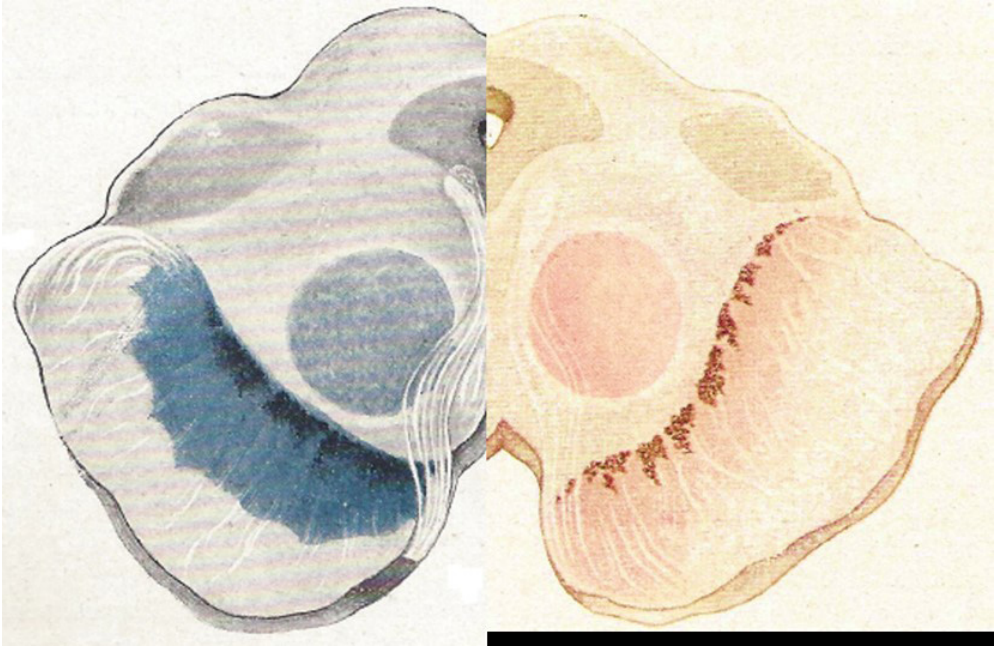


Fig. 2. The human nucleus ruber (red nucleus) stained for iron (left, Berlin blue reaction) and its natural appearance in a mesencephalic section (right). Note that the substantia nigra, in the foot of the brain section, shows the same phenomena (Burdach, 1822,"rother Kern" [7]).

Thus, red nucleus is not a "household" name, but it is based on its visual reality. It is also believed that the red nucleus looks pale pink due to the presence of iron in it. The cause of the pinkish appearance is the presence of a higher concentration of capillaries than the direct environment of the nucleus ("sehr gefässreiches", [39]), which is confirmed by the high amount of blood vessel alkaline phosphatase in this nucleus. Massion [37] denies this, but his figure demonstrates high vessel content. It is also characterized by the presence of a large amount of iron (**Fig. 2**) and high concentrations of vitamin B2 [14]. One should also note that this nucleus is one of the few that contains even higher concentrations of iron in Parkinson's dyskinesia [28] and of Parkin, a Parkinson's disease related protein [71]). As a result, this nucleus can also be noted microscopically and biochemically, which is used for colouration of the tissue, and as such it has intrigued these ancient neuroanatomists, also by its size and connections (see [39]). Microscopy brought the solution and it is now an ordinary mesencephalic large nucleus involved in cerebellar circuits (**Fig. 3**) and in spinal cord steering. The rubrospinal tract shows activity during automated, already

learnt, movements [23]. The red nucleus has been subdivided into a parvocellular part that derives the central tegmental tract (orange in **Fig. 3A**) and a magnocellular part, the origin of the rubro-spinal tract. Its rubro-spinal tract was for the first time described by von Monakow in 1883 [40]. Counterpart is the medial tegmental tract by which the nucleus of Darkschewitsch (**Fig. 3B**) is the most important contributor with the interstitial nucleus of Cajal and the nucleus of the fields of Forel [41].

The red nucleus is present in humans, all other mammals [20] and in birds. Amphibians, reptiles, and various fish do have a red nucleus. This review centres on comparing likeness in structure between nuclei of different organisms. Similarity between nuclei of different species has to be based on three arguments: likeness in localisation (topography), likeness in cell architecture and a likeness in connections of the nucleus. Nevertheless, such a similarity will not be absolute. We start with the rat and cat as mammal exponents, describe the human red nucleus to end with the pigeon. Note that reptiles and amphibians do have a "red nucleus", but it is considered a small and differently built nucleus. The primitive red nucleus is difficult to border in the ventral mesencephalon, but still does serve the connections between cerebellum via cerebellar nuclei and the spinal cord. It is omitted in this overview due to its cytological difference in similarity to other vertebrates, by its absence of olivary projections (anurans: frogs, toads, tree frogs) and the non-existence of cortical connections (quadrupedal reptiles). In lower vertebrates the presence of a red nucleus and its rubrospinal tract is linked to the presence of limbs or limb-like structures [12, 61].

The nuclei in the brainstem, including the red nucleus, have been classified as open and closed nuclei by their dendritic extensions towards other nuclei [30]. The magnocellular part of the red nucleus is considered a closed part, while the parvocellular red nucleus neurons are heavily involved in dendritic spread within the neighbouring reticular formation neurons. Borders of the capillary rich red nucleus can be established despite the parvocellular open structure (**Fig. 2**). The red nucleus produces, in origin, two output connections that derive from its parts: a series of connections that are grouped into a tract, which stays at the same side as the nucleus is placed and a series of connections that are fasciculated at the other side of the nucleus, its contralateral tract. Since the brainstem is bilaterally symmetric we do have four tracts, two crossed and two uncrossed. One side "should" contain a crossed and uncrossed tract.

The rat rubrospinal tract during development

Lakke's study in the *rat* [26] included also the development of the connections of the red nucleus [27]. The red nucleus in rat receives cortical information and is involved in the cerebellar and spinal systems. By its bulbospinal and rubrospinal tracts the red nucleus projects contralaterally to: the nucleus reticularis lateralis, the nucleus facialis, the nucleus interpositus, the nucleus vestibularis descendens, the nucleus cuneatus, and the spinal cord; ipsilaterally to the nucleus ventralis lateralis thalami (see [27] for references). The connection of the red nucleus to the nucleus olivaris inferior has been denied in the rat [55]. However, the parafascicular prerubral area, a diffuse nucleus directly above and partially aside of the nucleus ruber, around the fasciculus retroflexus and near the ventricle, does project to the olivary nucleus [54]. This parafascicular prerubral area is in the same position and contains the same function as a parvocellular red nucleus [53]. The rat's red nucleus tracts contain a crossed one for the spinal cord that reaches high (cervical) and low (lumbosacral) parts of the spinal cord [8].

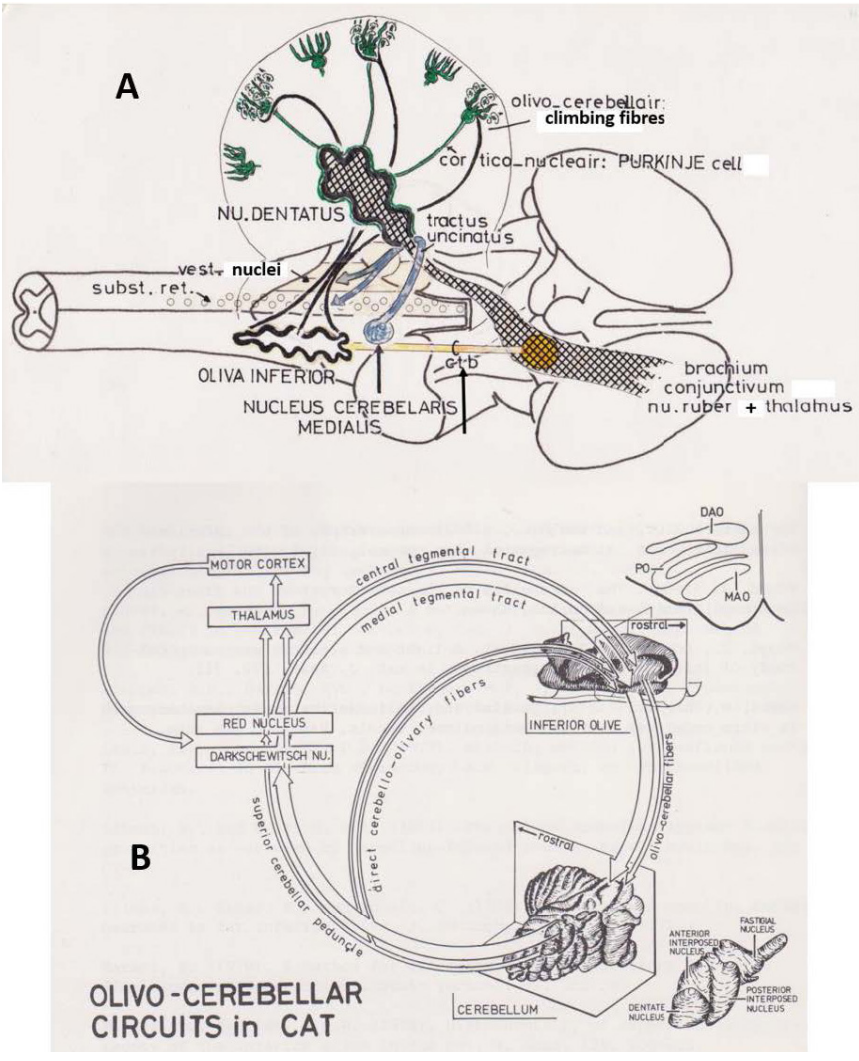
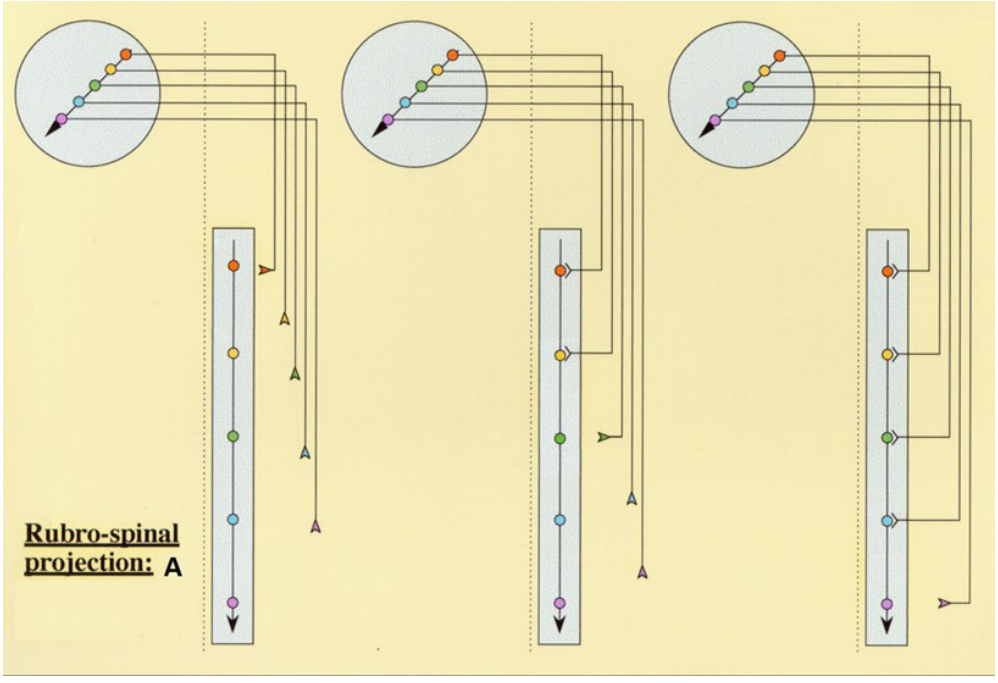


Fig. 3A. Overview of cerebellar connections with the tractus uncinatus in blue, brachium conjunctivum black-crossed and the central tegmental tract in orange (ctb arrow; fig. from exposition "cerebellum" Gesellschaft für Histochemie, 1983, Gargellen). **B**: The neural connections involved in the red nucleus by its participation in the olivo-cerebellar circuits, Darkschewitsch nucleus and inferior olivary complex of the cat. The inferior olive (top right) can be subdivided into three main parts: the dorsal accessory olive (DAO) the principal olive (PO) and medial accessory olive (MAO). Cells of the inferior olive project to the cerebellar cortex as climbing fibres. These fibres constitute the olivo-cerebellar tract. Within the cerebellar cortex the intrinsic connections relay the information towards the cerebellar nuclei (bottom right). The output system of the cerebellar nuclei is the superior cerebellar peduncle, which terminates in the contralateral red nucleus and the nucleus of Darkschewitsch. The cerebellar nuclei also project back to the inferior olive. A closed loop exists because both the red nucleus and the Darkschewitsch nucleus project back to the inferior olive by the central and medial tegmental tract respectively. The output of this closed loop is through axons of the cerebellar nuclei that project on the thalamus (fig. [31], courtesy J.Voogd).

Following injections of horseradish peroxidase or wheat germ agglutinin-horseradish peroxidase conjugate into the spinal cord, at different levels and at different gestational ages the rubrospinal tract development could be followed (**Fig. 4**). By embryonic day 17 (E17) fibers from all subdivisions of the nucleus ruber have started their descent towards the spinal cord. On E18 fibers from the ventrolateral red nucleus arrived into the lower cervical spinal cord, while those from the caudal nuclear area terminate into the lower thoracic spinal cord. At E19 fibers from the dorsomedial red nucleus and from the parvicellular area have just reached the cervical spinal cord, while fibers from the ventrolateral and caudal areas have appeared into lower thoracic levels. At E21 fibers from the dorsomedial red nucleus have turned up into the lower cervical spinal cord. Fibers from the ventrolateral and caudal nucleus finished their descent through the lumbosacral spinal cord during the first three postnatal days. During their descent the rubrospinal fibers are limited to the white matter of the spinal cord (**Fig. 4**). In general, early descending fibers originate from neurons located caudally and ventrolaterally, and later descending fibers from neurons located more rostrally and dorsomedially in the magnocellular red nucleus. The sharp distinction of the connections between magnocellular and parvocellular parts of the red nucleus as kept by the overviews [1, 42]), is less present in the rat in the course of its development and during its maturity [23].



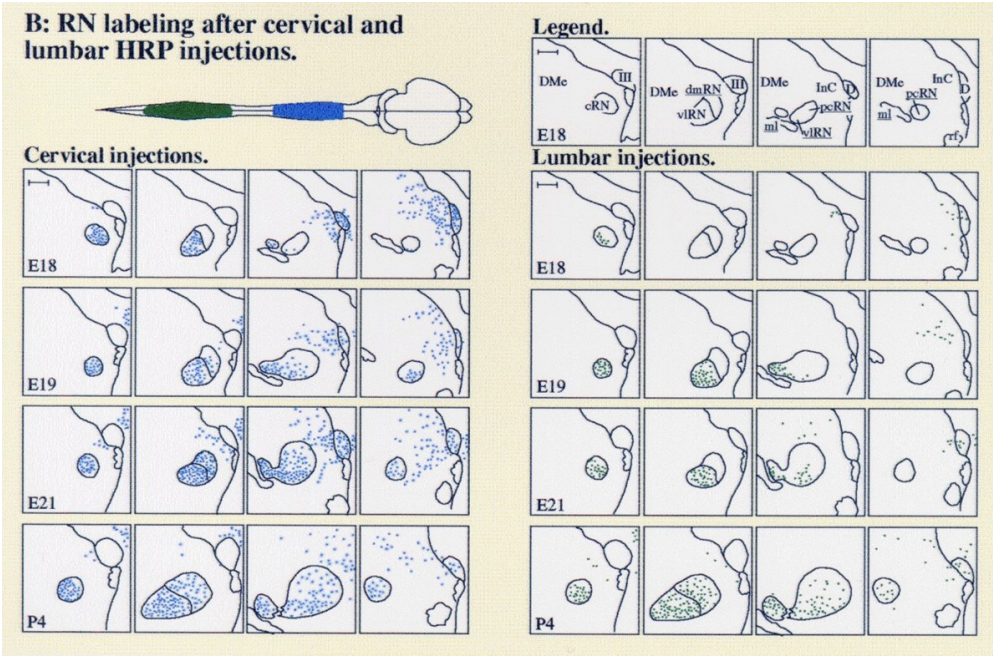


Fig. 4. In **A** the descending spinal fibres of the red nucleus are shown at their topography in the rubro-spinal tract during descent. **B**, shows the labelling of the red nucleus after HRP injections at cervical and lumbar levels (courtesy E. Lakke; Legend: III, oculomotor nucleus; DMe, nucleus reticularis mesencephalicus profundus; InC, nucleus interstitialis Cajal; D, nucleus Darkschewitsch;, ml lemniscus medialis; rf, fasciculus retroflexus).

Red nucleus and tracts in humans as well as olivary hypertrophy

In humans the steering of motor activities had been subdivided in pyramidal and extrapyramidal guiding or differently said a direct cortical influence (pyramidal) and an indirect one (extrapyramidal). The indirect cortical steering (Bechterew, 1885 [2]) should go over the red nucleus as was deduced from animal and clinical research as described by Probst [49] for the central tegmental connection. The human nucleus contains also large and small cells. It was Verhaart (1889-1983; for cv see [66]), who unravelled the human nucleus ruber connections due to his comparative neuroanatomical approach. Verhaart [62, 63] finalized his results on the red nucleus in "The central tegmental tract" in 1949 [64]. This uncrossed tract was exclusively related to the red nucleus. The crossed rubrospinal tract in humans was found inconstant and of "slight dimension", and "through the development of the frontal part of the red nucleus and the regression of the caudal part, this nucleus has changed its character from a pre-eminently motor nucleus to a nucleus connected to the olivocerebellar system" (Verhaart, [63]). Simply said, part of the nucleus was reduced compared to other mammalian red nuclei. Its crossed spinal projecting part was minimally present and hardly reached the start of the cervical spinal cord. Sie Pek Giuk [56], working at Verhaart's department, showed that 20% of the myelinated red nucleus fibres originated in the magnocellular part. "In the bipedal human, the magnocellular red nucleus is rudimentary" [43]. This overstated

claim has been contradicted by tractography studies on 100 persons in the Human Connectome Project, in which a clear localisation of the human magnocellular part was encountered: “note that the magnocellular regions appear well delineated in the upper slices located dorsally” [9].

Several publications have been considering the cooperation between the corticospinal and rubrospinal tracts. These studies use corticospinal tract damage also in humans (for overview see [44]). Lesions in the animal red nucleus are compensated by the corticospinal tract and by damage of the corticospinal tract recompense has been noticed in the cortico-rubro-spinal connections. In upper limb steering the red nucleus is responsible for pronation, while the cortico-spinal tract relates to arm reach and hand grip. Since in humans the rubro-spinal tract does not reach (below) cervical levels, it is puzzling that the red nucleus is still involved in improvement of the mobility of patients with cortico-spinal tract and spinal cord damage [42].

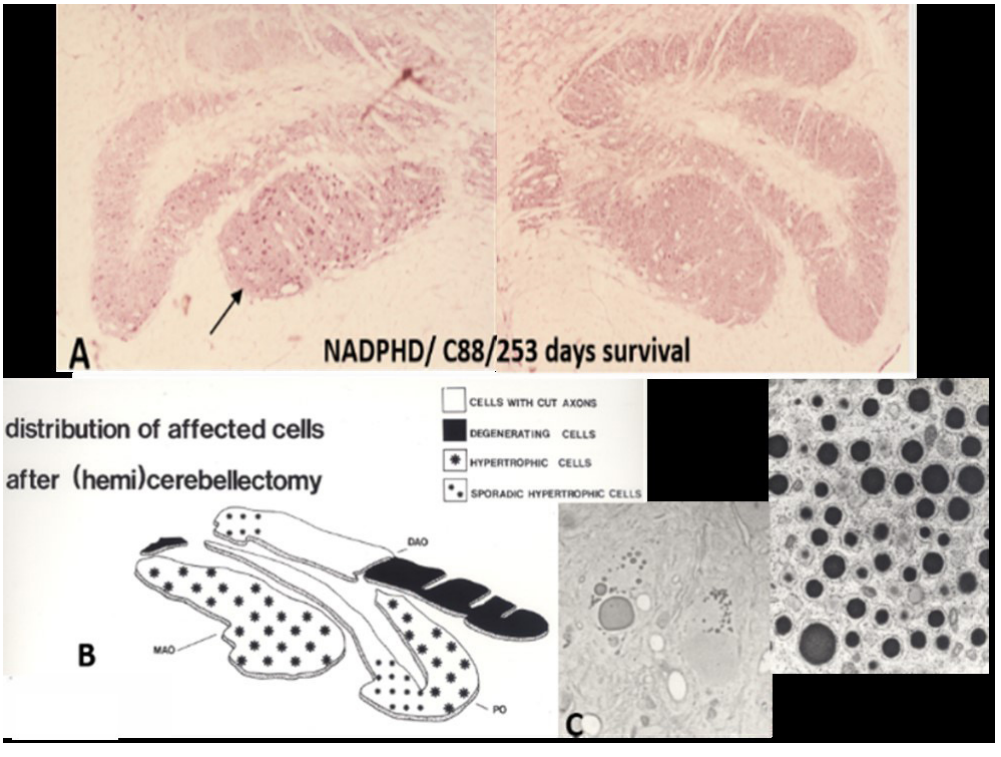


Fig. 5. Experimentally induced olivary hypertrophy in the cat. **A**: Increased enzymatic activity of NADPHD after a survival time of 253 days is shown after a hemicerebellectomy. Present in the cat rostro-lateral medial accessory olivary (MAO) are hypertrophic neurons, arrow. **B**: overview of the areas containing hypertrophic olivary neurons together with sporadic hypertrophic areas in the inferior olive. **C**: Light microscopic section treated for the anhydride technique. Positive dense globular inclusions are noted within the hypertrophic neurons indicating that accumulation of protein-bound carboxyls could occur within the hypertrophic cells in the cat [32]. **D**: The electron micrograph shows the osmiophilic globular inclusions within the cat extended granular endoplasmic reticulum (courtesy AJP Boesten, see [5]; adapted fig., courtesey [33]).

Olivary hypertrophy. Sometimes luck is at your side. Cleaning the loft of the Leiden Neurology Department brought out the series of sections of the cats studied by Rademaker. Verhaart found the olivary hypertrophy in these series, e.g. in the cat Marie-Antoinette (Rademaker [50] studied cerebellar posture and named all his experimental cats). Within Verhaart's group, the cerebello-rubro-olivary hypertrophy was established as caused by cerebellar and cerebellar nuclei deficits and it was the basis for Verhaart and Voogd's [65] experimental results [5]. Olivary hypertrophy is judged a combined retrograde and antegrade transneuronal reaction, because the direct cerebello-olivary projections, the dentate-rubral projections and the Darkschewitsch-olivary projections (**Fig. 3**) coincide in the hypertrophic olivary areas as studied in cats (**Fig. 5**). Palate myoclonus has been regularly related to olivary hypertrophy (for overviews, see [13, 16]). In short, lesions or haemorrhages of the brainstem or cerebellum are nearly always related to olivary hypertrophy, which is generally considered a "degeneration" of the inferior olive, but it is in fact hyperactivity of the olivary neurons. The discovery of the reduction of serotonin in the hypertrophic inferior olive supports its hyperactivity (see [33] for more (enzyme)histochemistry and references). The detection of this serotoninergic effect opened a new medical approach for myoclonus using the serotonin precursor 5-hydroxytryptophan. The detection of the relation between typical lesions and olive hypertrophy was already described in 1882 by Meyer [38]. At first publications restricted the lesions to damage of the tegmentum pontis with homolateral inferior olive hypertrophy, later on to cerebellar lesions, always involving the dentate nucleus, producing contralateral inferior olive hypertrophy. Bilateral inferior olivary hypertrophy was described after a shot wound involving lesions of the right-sided dentate nucleus and right-sided tegmentum pontis [61] supporting the earlier cerebellar findings. The correlation between palate myoclonus and these types of lesions and inferior olive hypertrophy came late. From around 1930 on several tens of articles have been published relating palate myoclonus to inferior olivary hypertrophy (see [33]).

In 1967 Jean Massion [36] published an overview of the mammalian red nucleus. The article had two main parts: an anatomical and a physiological one. Its anatomical description was mainly based on the results of early chromatolysis or the late neuronal changes, consisting of atrophy and loss of cells or silver degeneration studies carried out by several researchers. The anatomical results noticed a series of uncertainties that asked for more research and most research concerned the magnocellular part and clearly less the parvocellular part. His summary of the anatomical connections had been generally accepted (**Fig. 6**).

Its physiological part concludes that "the rubrospinal tract exerts a multiple action on the spinal cord. Through the intermediary of interneurons, it excites alpha moto-neurons and also gamma motoneurons (to the static fusimotor fibers) of the contralateral flexor muscles. At the same time, it inhibits the alpha fibers and the static fusimotor fibers of the contralateral extensor muscles. Moreover, it facilitates a whole set of inhibitory and excitatory spinal reflexes by acting directly on interneurons involved in these reflexes. Furthermore, the rubrospinal tract is responsible for the facilitation of the cells of origin of the ventral spinocerebellar tract. It also controls activity in the primary afferents as these enter the spinal cord by means of presynaptic inhibition" [36]. The ruber electrophysiological results in those days belonged to the high-quality research. Thus, rubrospinal effects are activation of contralateral flexion and inhibition of contralateral extension.

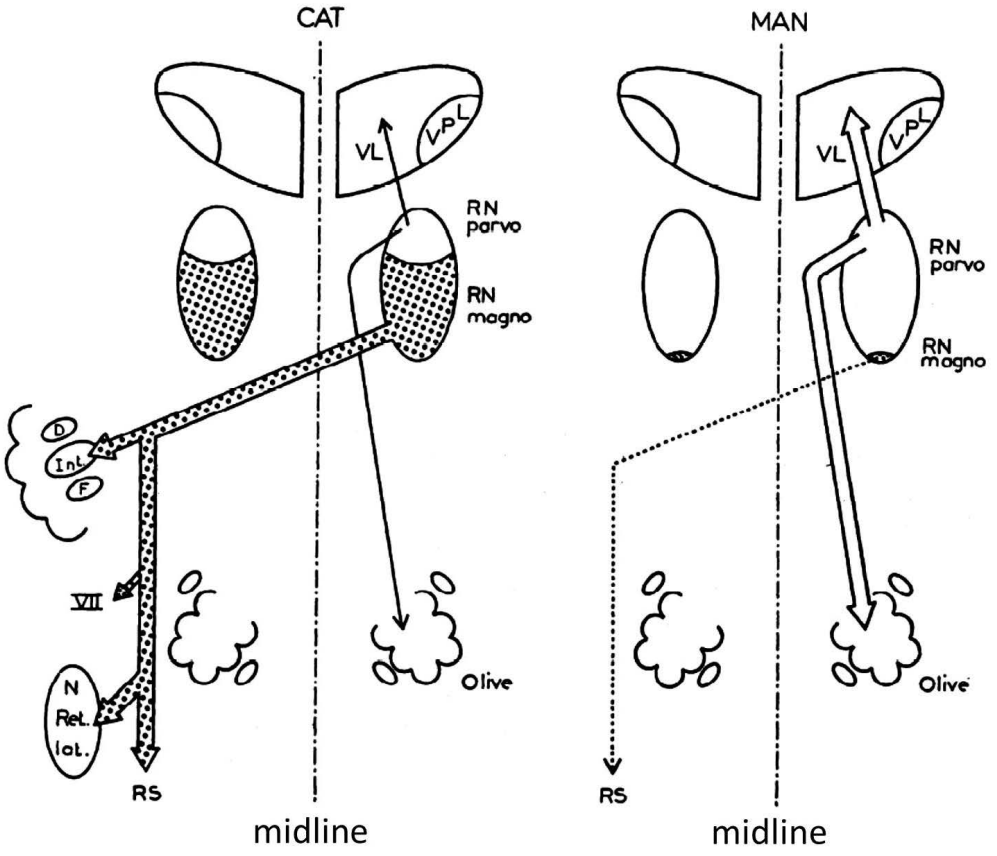


Fig. 6. Comparison of efferent connections of the red nucleus in cat and in man. RN Parvo, red nucleus, parvocellular part; RN magno, red nucleus, magnocellular part; RS, rubrospinal tract; VL, ventrolateral nucleus of the thalamus; VPL, ventroposterolateral nucleus; D, dentate nucleus; Int, nucleus interpositus; F, fastigial nucleus; N Ret. Lat, lateral reticular nucleus (adapted fig.2, [36])

Red nucleus and tracts in birds

The capillary rich red nucleus in the *pigeon* [68, 72] has to a certain degree a different cytoarchitecture that is though linked to that of mammals. Large cells (58 μm; 40-50 according to [69] pigeon; 70-100 mu in the chicken, [45]), medium cells (39 mu) and small cells (25 mu) are counted by Johnston [21] in the pigeon that compare to the red nucleus counts of Ramon y Cajal (1909-1911, [10]). "Large, medium and small-sized cells appeared to be equally distributed throughout each level of the nucleus. No noticeable sub grouping of cells, such as to constitute the sub groupings delineated in some mammals, was observed" [21]. Nevertheless a weaker subdivision of a magnocellular area (apex and ventrolateral part) has also been discerned. The rest of the nucleus has been dominated by medium and small cells, called a parvocellular area [69]. In the chicken a clear magnocellular and parvocellular area can be discerned [45]. The guinea pig study of Robak et al. [52] supports that the smaller cell group belongs to spiny and a-spiny interneurons, as interneurons are also known from the

rat [51]. Such a clear statement is to the best of my knowledge not found for the avian red nucleus. Although histochemistry of the metabolism of the different types of neurons can discern between large and medium chicken red nucleus neurons, such is not viable for the small cells [45]. Often interneurons are inhibitory, but GABA-like immunoreactivity is absent in the red nucleus of the pigeon [11]. Therefore, no arguments for avian interneurons can be taken from literature.

The avian rubrospinal tract crosses the midline and descends in the brainstem before shifting to the lateral part to reside in the dorso-lateral funiculus of the spinal cord. It arises from all cell sizes of the red nucleus. The avian rubrospinal tract reaches all levels of the spinal cord. Within the spinal grey this tract terminates in the layers 4 and 5, low in the dorsal horn and its intermediate area. An uncrossed rubrospinal tract has not been found in birds. The red nucleus receives contralateral lateral-cerebellar nucleus fibres and from the contralateral dorsal column nuclei [68, 69]. A restricted projection to the red nucleus relays from the hyperstriatum accessorium of the anterior Wulst. Thus a cortical/pallial projection is present. A much denser projection arises from the caudal part of the nucleus principalis precommissuralis and the medial part of the medial spiriform nucleus, organizing the thalamic connection. The red nucleus projects directly to the contralateral cerebellar cortex as mossy fibres. A direct olivary connection is not present, but should pass over the thalamic area [69]. The red nucleus in birds facilitates contralateral flexor and inhibits contralateral extensor activity like in mammals and it is involved in execution of learned motor behaviour [21].

The mallard superspinal nucleus is localized at the transition of spinal cord and brainstem. It innervates part of the craniocervical muscles, involved in head posture during its movements. Upward tilting muscles like the m splenius capitis and m. complexus and muscles for bending, e.g. m. rectus capitis ventralis, are steered by the superspinal nucleus. The ruber projects bilaterally to this superspinal nucleus. This rubro-"cervical" connection is somewhat restricted, but undeniable [59]. Not only the nucleus ruber, but also the reticular mesencephalic formation dorsal to the red nucleus and around the oculomotorius nucleus participate in this connection [60].

The direct spinal-rubral loop

The detection of a direct spinal influence on the magnocellular red nucleus was for the first time supposed by Kerr [24]. Its confirmation was obtained by the physiological cat studies of Padel and Jeneskog ([46, 47]; see also [48]). Spinal information will reach the magnocellular part of the red nucleus using fibres present in the cat's lemniscus medialis to ascent. Stimulation of these lemniscal fibres produces powerful monosynaptic EPSP's and disynaptic IPSP's on nearly all magnocellular red neurons. The magnocellular red nucleus is involved in several loops: direct spino-rubro-spinal loop, spino-cerebello-rubro-spinal loop and the spino-cortico-rubro-spinal loop. The rubro-spinal connection is involved in activating flexor motor activity and inhibition of extensor activity, but its spino-rubral part mainly in the sending of information on the perturbation of ongoing movements [48].

Note that sparse rubral ascending degeneration is found in the human red nucleus in Wallenberg syndrome related to lemnicus medialis degeneration (central tegmental tract was degeneration free), but not after C1 transverse lesion ([34] its **Figs. 4** and **5**).

Special scientific advances

The red nucleus and association cortex.

Critical checking of 20 patients with head and neck cancer from a far larger group using ^{18}F-FDG (radioactive fluordeoxyglucose) in a PET (positron emission tomography) study showed a difference in the metabolic activity of the left and the right red nucleus in humans. The results demonstrated that the right red nucleus is more intensely related to cortical association network areas or hubs [17] compared to the left red nucleus. The left red nucleus in its turn has a more intense relation with the cerebellum compared to the right one (**Fig. 7**). This functional asymmetry could only be detected due to a newly developed high-resolution semiconductor PET [18].

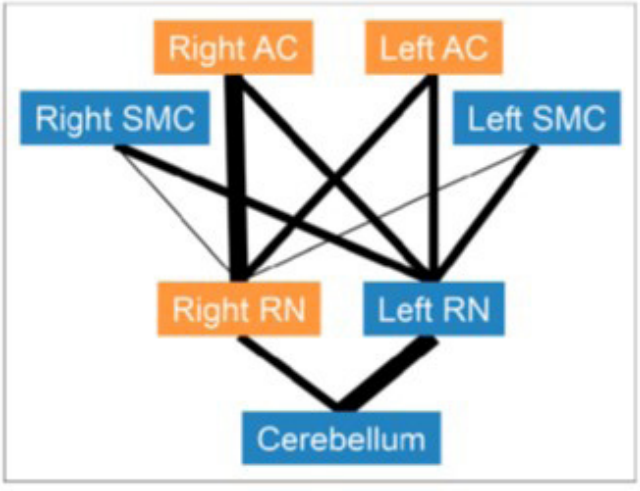


Fig. 7. Width of lines represents degree of association between 2 regions. AC, association cortex; RN, red nucleus; SMC, sensimotor cortex [18].

The red nucleus and migraine.

Migraine has also been coupled to brainstem malfunctions. Migraine without aura has been related to the red nucleus and the substantia nigra using resting-state functional magnetic resonance imaging (fMRI). The functional connectivity of the red nucleus showed reduced left red nucleus-based functional connectivity with the left middle frontal gyrus, reduced right red nucleus-based functional connectivity with the ipsilateral superior parietal lobe, and left increased functional connectivity with the ipsilateral cerebellum. The results also demonstrated significantly decreased right substantia nigra-based functional connectivity with the right postcentral gyrus, left parietal lobule, and left superior frontal gyrus [19]. It should be noted that this article also describes functional asymmetry of the red nuclei.

Leigh syndrome, SURF1 mutations and olivary hypertrophy.

Leigh mitochondrial syndrome can be related to cytochrome c oxidase deficiency. This enzyme is functional in mitochondria and is a complex of several units. The mitochondrial genome and the nuclear genome produce 3 and 10 units respectively. The assembly is done by *SURF1* COX genes. Mutations of the *SURF1* produces the Leigh syndrome in children and sometimes in adults. In children it is lethal. Magnetic resonance studies show in most cases olivary hypertrophy and often subthalamic nucleus disturbances

[57]. Bilateral olivary hypertrophy is also reported in children with Leigh syndrome [4]. Several other diseases also produce olivary hypertrophy. Cerebrovascular diseases including haemorrhage, infarction, and vascular malformations are the most frequently reported cases in both types of olivary hypertrophy, 62% unilateral and 30% bilateral hypertrophy [25].

The red nucleus and Pou4f1.

The mouse red nucleus contains a strong presence of *Pou4f1* that is responsible for a precise differentiation pathway. This transcription factor with a DNA binding of the POU domain is related to its specification. In *POU4f1*$^{-/-}$ mice red nucleus cells do not survive and fail to correctly contact its peripheral aims [70]. Despite the loss of function in the transgenic mice Pou4f1$^{TauLacZ/+}$ embryos compared to Pou4f1$^{TauLacZ/TauLacZ}$ embryos, it was shown that the red nucleus was still present. However, its cellular organisation was disturbed, the nucleus worse bordered and a delay in radial migration occurred (**Fig. 8**). Moreover, the axons did descent in the spinal cord but were defasciculated. *POU4f1* is not necessary for the generation of the red nucleus, but co-determines its development, connections and maintenance [35].

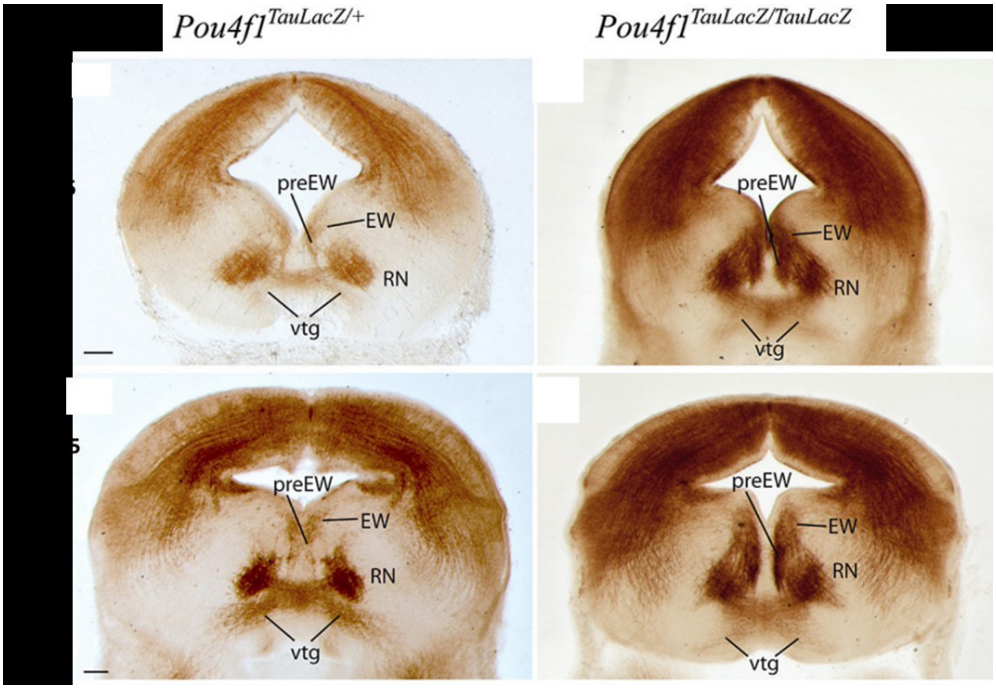


Fig. 8 . Coronal mesencephalic sections in Pou4fTauLacZ/+ and Pou4fTauLacZ/TauLacZ embryos processed by immunohistochemistry. The figure contains the embryonic stages: E14.5 and E15.5, earlier stages are not shown here. The normal generation of the RN and its projections in the control embryos is presented at the right. Left, the RN development in the mutant embryos showed a clear delay in radial migration. The RN displayed a certain spatial disorganization. Abbreviations: EW, Edinger-Westphal nucleus; RN, red nucleus; preEW, pre-Edinger-Westphal; vtg, ventral tegmental decussation. Scale bars=150 mm. (Fig. adapted from [35], part of their fig. 1).

The red nucleus and restless legs syndrome.

The red nucleus has been related to restless legs syndrome in various articles. A magnetic resonance study accompanied by a meta-analysis shows that in these patients high iron concentrations have been detected in caudate, putamen and red nucleus [3]. During a combined limb movement and sensory leg discomfort period, patients showed activity in the cerebellum and thalamus. Additional activation in the red nuclei and brainstem close to the reticular formation was noticed. If only sensory leg discomfort was present bilateral activation of the cerebellum and the contralateral thalamus, but no involvement of the red nucleus was observed [6]. Seemingly the restless legs syndrome is coupled to the dentate-ruber-olivary-cerebellum loop in humans. In rat lesions, the role of the cerebello-rubral-spinal loop is supported in restless legs syndrome [15].

Conclusion

Historical overviews show that in humans the uncrossed rubral connections are robustly developed. Mutually in rats, due to the area parafascicularis prerubralis, and in cats both uncrossed and crossed tracts are present, while in birds the crossed rubro-spinal tract is exclusively utilized, demonstrating the different species evolutionary choice. Localization and partly the cellular sizes of the red nuclei are comparable in mammals and birds. The presence of red nucleus interneurons in birds needs further research. Functional activities concern contralateral flexor activation and contralateral extensor inhibition. Moreover, the rubro-spinal tract is active when automated, already learnt, movements have to be performed and spino-rubral effects concern perturbation of ongoing movements. The occurrence of asymmetry between left and right red nuclei has been established by fMRI and PET studies. Olivary hypertrophy not only occurs due to brainstem/cerebellar deficits and vascular infarctions, but also because of mitochondrial genetic mutations. The red nucleus is involved in migraine and in restless legs syndrome. Human red nucleus activity after spinal cord damage to improve mobility of these patients surprises.

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