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ORIGINAL ARTICLE

The corticotegmental connectivity as an integral component of the descending extrapyramidal pathway: novel and direct structural evidence stemming from focused fiber dissections

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Abstract
This study opts to investigate the thus far ill-defined intra-hemispheric topography, morphology, and connectivity of the extrapyramidal fibers that originate from the frontoparietal cortex and project to the tegmental area and to explore structural correlations to the pyramidal pathway. To this end, twenty normal adult, formalin-fixed cerebral hemispheres were studied through the fiber micro-dissection technique. Stepwise and in-tandem medial to lateral and lateral to medial dissections were carried out in all specimens. The cortical termination of the fibers under investigation was carefully defined, and their entry zone at the tegmental area was meticulously recorded. We consistently identified the corticotegmental tract (CTT) as a distinct fiber pathway lying in the white matter of the genu and posterior limb of the internal capsule and travelling medial to the corticospinal tract (CST) and lateral to the thalamic radiations. The CTT exhibits a fan-shaped configuration and can be classified into three discrete segments: a rostral one receiving fibers from BA8 (pre-SMA, frontal eye fields, dorsal prefrontal cortex), a middle one arising from areas BA4 and BA6 (primary motor cortex and premotor cortex), and a caudal one stemming from areas BA1/2/3 (somatosensory cortex). The anatomical location, configuration, trajectory, and axonal connectivity of this tract are attuned to the descending component of the extrapyramidal system, and therefore, it is believed to be implicated in locomotion, postural control, motor inhibition, and motor modification. Our results provide further support on the emerging concept of a dynamic, parallel, and delocalized theory for complex human motor behavior.

Keywords Corticotegmental tract · Extrapyramidal · Premotor · Prefrontal · Motor · Fiber dissection

Introduction

The word “tegmentum” derives from the Latin verb “tegere,” which means “to cover.” This term was adopted by early neuroanatomists to describe the part of the midbrain that extends dorsal and therefore “covers” the crus cerebri, i.e., the mesencephalic structure that consists of the corticospinal and corticobulbar pyramidal fibers. The pivotal topography of the tegmentum—lying between the forebrain and brainstem—underlies its crucial role as a gateway for the non-pyramidal motor routes and the ascending sensory pathways.

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The term "extrapyramidal motor system" coined by Johann Prus in 1898, is used to describe a basic and integral component of the human motor network primarily formed by corticofugal fibers that travel through the tegmental area, as opposed to the ventrally allocated pyramidal tracts [5]. The very anatomical organization and functional parcellation of the human extrapyramidal system has attracted interest for over a century. In this vein, Probst, Hoche, and Dejerine were among the first to study the extrapyramidal system and succeeded in demonstrating through the Marchi technique the existence of fibers stemming from the frontal area and projecting toward the mesencephalic reticular formation [38]. In a step further and during the second half of the twentieth century, cortico-rubro-spinal and cortico-rubro-cerebellar fibers have also been identified as extrapyramidal pathways by a number of studies [3, 15, 16, 33, 42]. More recently, the presence of corticomesencephalic and corticotectal tracts has been well documented in animal studies but has not been as yet demonstrated in the human brain [10, 11].

In the modern neuroscientific era, the advent of DWI-based tractography has indeed blazed new trails in our endeavor to verge toward a more refined understanding of the human connectome. It has further paved the way to combine this fast, in vivo but indirect technique of virtual fiber dissection with the more traditional, direct method of blunt white matter anatomical dissection, with the aim to improve the sensitivity and specificity of data acquisition. However, and in contrast to the thoroughly investigated pyramidal fibers of the corticospinal and corticobulbar tracts, the relevant literature on the intrahemispheric topography of the descending extrapyramidal fibers within the white matter of the cerebral hemisphere is scarce. With this in mind, we strived to investigate and record the system of fibers that mainly stem from the frontoparietal cortex and travel within the internal capsule before blending into the tegmental area. The term "corticotegmental tract" (CTT) is collectively used to include all the fiber pathways that meet these topographic prerequisites and hence stands as an anatomical equivalent of the descending extrapyramidal pathways.

We intentionally opted to use the white matter fiber microdissection technique as our stand-alone method of investigation since it has been proven to extrapolate safe results on the anatomy and connectivity of poorly understood white matter pathways and because it allows for the comprehension and conceptualization of the three-dimensional anatomy in contrast to the two-dimensional perception offered by both histopathological and tractographic studies. While the inherent perplexity of the corticotegmental network is given, our overreaching goal is to offer a solid macro-anatomical overview of the corticotegmental fiber system for theoretical and clinical use. To our knowledge, this is the first white matter dissection study in the relevant literature to focus on the intricate anatomy of the corticotegmental pathway as a prominent component within the human extrapyramidal system.

Materials and methods

After approval from the Bioethical Committee of the Medical School of the National and Kapodistrian University of Athens, twenty cadaveric normal adult cerebral hemispheres (10 right, 10 left) previously fixed in a 15% formalin solution for a period of 2 months were treated with the Klinger's technique and were subsequently dissected using the fiber-microdissection technique. Prior to the dissection process, the brainstem was dissected at the level of the superior colliculi and was studied later on, separately from the rest of the specimen. At this axial level, the "tegmental entry zone (TEZ)" was defined as the area of entrance of the CTT fibers in the tegmentum.

The basic surface landmarks of the lateral and medial aspect of the hemispheres were identified and recorded for orientation purposes prior to dissection. The precentral, postcentral, and superior frontal gyri were all marked as they constitute the dorsal termination zone of the CTT. The vertical line passing through the anterior commissure was used to demarcate the SMA from the pre-SMA. Additionally, the diencephalic and mesencephalic structures, such as the superior and inferior colliculi, the thalamus and the stria terminalis, the cerebellar peduncle, and the posterior commissure, were used as orientation landmarks during the dissection.

Given the spatial distribution of the corticotegmental fibers described by previous DTI studies, medial to lateral dissections were initially carried out in all specimens. The dissections followed a meticulous stepwise manner with special attention paid to the structures adjacent to the central core and superior aspect of the tegmentum. During the medial to lateral dissections, the spatial relationship of the corticotegmental fibers to the thalamus, caudate nucleus, callosal radiations, anterior thalamic peduncle (ATR), and frontocaudate tract (FCT) was recorded.

Upon completion of the medial to lateral process, all specimens were subsequently dissected in a lateral to medial fashion with the aim to study and record the spatial relationship of the CTT to the superior longitudinal fasciculus (SLF), lentiform nucleus (LN), internal capsule (IC), and corticospinal tract (CST). In all specimens, the termination pattern of the CTT was carefully traced in the frontoparietal area, and the respective Brodmann's areas were recorded. In addition, the topography of the corticotegmental fibers was recorded in the TEZ according to their cortical origin.

At the last steps of the procedure, the CTT and CST were progressively dissected free from the rest of the hemisphere and differentiated from each other with the purpose of juxtaposing the pyramidal and extrapyramidal fiber topography and trajectory. In 5 hemispheres, the diencephalic and mesencephalic structures were also dissected free from the specimen to study and illustrate the ventral allocation of the CTT fibers and their relationship with the thalamic, hypothalamic, and mesencephalic structures.

At the end of the procedure, the brainstem that was initially removed from the hemisphere at the level of the superior colliculus was dissected in a lateral to medial fashion and under high magnification. The fibers of this region were categorized into consecutive layers, starting from superficial to deep, and were subsequently superimposed on the tegmental entry zone.

Our dissection instruments were various-sized microforceps, microscissors, and micro-spatulas. During the study, many photos were obtained from different angles to document and illustrate the regional anatomy of interest.

Results

Medial to lateral dissections

Upon removing the cortical grey matter, we reveal the superficial U-fibers along with the cingulum bundle. Progressive dissection of the u-fibers, superior arm of the cingulum and corpus callosum exposes the anatomy of the lateral ventricle in a way that the callosal radiations can be appreciated. The caudate nucleus is evident and its thin ependymal covering is removed. The grey matter of the caudate must be meticulously dissected to identify a thin layer of fibers that lies in the white matter just lateral to the nucleus and is formed by the thalamic radiations and the frontocaudate tract. Following the careful removal of this white matter layer, we gradually reveal the corticotegmental fibers. We follow these fibers in their dorsal direction up to their termination area that is recorded to extend from the posteromedial part of the superior frontal gyrus to the superior aspect of the postcentral gyrus. Following these fibers in their ventral direction, we see them entering the tegmentum posterior to the substantia nigra, in what we define as the tegmental entry zone (TEZ).

Along their course and trajectory, the corticotegmental fibers are seen to travel in the white matter of the genu and posterior limb of the internal capsule with no fibers traced in the anterior limb of the internal capsule (ALIC). The fibers of the ALIC lie anterior to the CTT and substantia nigra when entering the cerebral peduncle. The CTT's entry zone to the tegmentum was consistently located at the lateral half of this area. Interestingly, during the dissections, a cortico-topic distribution of the CTT was revealed. More specifically, the majority of the CTT fibers stemming from BA8 were recorded to reside to the anterior part of the TEZ, the majority of CTT fibers arising from BA4 and BA6 to the middle part and the fibers from BA1/2/3 to the posterior part of the TEZ.

Lateral to medial dissections

We included latero-medial dissections to give a complete anatomical perspective of the CTT. Upon removing the cortical grey matter and superficial U-fibers of the frontoparietal area, we expose the fibers of SLF. At the level of the insula and following progressive dissection of the extreme/external capsules and claustrum, we reveal the silhouette of the lentiform nucleus. The posterior part of the lentiform nucleus is removed to gain access to the genu of the internal capsule that comprises the corticospinal tract (CST) as its most superficial layer. The fibers of the CST are seen to project toward the cerebral peduncle, lying anterior to the substantia nigra. These fibers are meticulously removed to reveal the fibers of the CTT that course in a different trajectory, traveling in a plane posterior to the substantia nigra when entering the tegmental area.

Morphology of the CTT and its spatial relationship to adjacent fiber tracts

As previously demonstrated, CTT fibers reside in the white matter of the genu and posterior limb of the internal capsule. The CTT can be traced medial to the fibers of the CST and lateral to the fibers of the thalamic radiations. While the fibers of the CST maintain a postero-superior to antero-inferior trajectory, radiating from the precentral gyrus to the cerebral peduncle, the trajectory of the CTT varies in the rostro-caudal axis. The caudal fibers exhibit a straight superior to inferior configuration while the rostral fibers adopt a lazy-S morphology, bending caudally and then inferiorly before entering the tegmentum. Additionally, the rostral aspect of the CTT was always bulkier in comparison with the caudal one.

Cortical termination areas of the corticotegmental fibers

The fibers of the CTT could be traced in the middle and posterior part of the superior frontal gyrus (BA8 and BA6 respectively) in 100% of the studied specimens. These areas correspond to the dorsal premotor cortex, SMA, pre-SMA, and frontal eye field (FEF). Consistent terminations (100% of the specimens) were also evident in the superior part of the precentral gyrus and supero-anterior part of the paracentral lobule (BA 4), i.e., the primary motor cortex. In 65% (13/20) of cases, fibers of the CTT were tracked in the superior part of the postcentral gyrus and the supero-posterior part of the paracentral lobule (BA 1/2/3), areas that functionally correspond to the somatosensory cortex.

Interestingly, we did not observe hemispheric asymmetries regarding the CTT's morphology, topography, or connectivity. The cortical terminations, segmentation pattern, morphology, and putative functional role of the corticotegmental fibers are summarized in Table 1.

Introducing the "tegmental entry zone" (TEZ) and tracking the infra-tegmental distribution of CTT fibers

In all cases, the CTT reached the superior aspect of the tegmentum (level of the superior colliculi) in its lateral half, in contrast to the thalamo/hypothalamic-tegmental fibers that enter this area mainly (but not solely) in its medial half. CTT fibers stemming from BA8 were located anteriorly in this lateral tegmental zone, whereas fibers from BA4 and BA6 and BA1/2/3 in the middle and posterior parts respectively. The term tegmental entry zone (TEZ) was coined for this area and is used to stress the fact that this region does not represent the termination area of the CTT.

By dissecting the brainstem in a lateral to medial direction, we were able to differentiate and classify four layers of white matter fibers. The first and most superficial layer consists of fibers projecting toward the superior cerebellar peduncle and lateral aspect of the floor of the fourth ventricle. These fibers were recorded to travel in 45° angle. The second layer is formed by fibers radiating toward the superior/inferior colliculi complex and superior aspect of the floor of the fourth ventricle (area of the locus coeruleus). These fibers share an orientation of 30°. The third layer includes longitudinal projecting fibers running in a supero-inferior trajectory, from the tegmental area toward the lateral funiculus. Finally, the fourth and deepest layer exhibits fibers coming from the superior cerebellar peduncle and decussating toward the contralateral tegmental area, in the ventral tegmental decussation. By superimposing these four layers into the TEZ area, we were able to put together a table showing the origin and projection of fibers categorized in 11 distinct zones (Table 2).

Table 1 Anatomical morphology, parcelation, and functional role of corticotegmental fibers.

Cortical terminations	Brodmann areas		
	BA 1/2/3 Functional area	BA4 and BA6	BA8
	Sensory xortex (66%)	Primary motor cortex/ premotor cortex/SMA (100%)	Pre-SMA/FEF (100%)
Segmentation of corticotegmental fibers	Caudal corticotegmental tract	Middle corticotegmental tract	Rostral corticotegmental tract
Fiber trajectory	Fibers originate from postcentral gyrus, travel along the posterior limb of the internal capsule and terminate at the dorsolateral tegmentum	Fibers originate from precentral gyrus/SMA and premotor cortex, travel along the genu of the internal capsule, medial to the CST and terminate at the mediolateral tegmentum	Fibers originate from pre-SMA and FEF travel along the genu of the internal capsule, medial to the CST and terminate at the ventrolateral tegmentum
Implicated pathway	Ascending reticular arousal system (ARAS)/corticorubral tract/cortico-rubro--cerebellar tract	Corticoreticular tract	Corticomesencephalic tract
Midbrain target	Reticular formation/red nucleus	Reticular formation	Directly through medial longitudinal fasciculus to nuclei of CN III and CN IV Indirectly to CN VI nucleus through PPRF (paramedian pontine reticular formation)
Possible functional role	Input of sensory stimuli to reticular formation; maintenance of arousal; excitation of flexor muscles and inhibition of extensor muscles	Motor learning, gait, and posture programming	Oculomotor function, conjugate eye movements

CN cranial nerve, *CST* corticospinal tract, *FEF* frontal eye fields, *SMA* supplementary motor area

Discussion

The extrapyramidal system is typically divided in a cortical-basal ganglia-cortical loop and a descending corticofugal component [1, 14, 38]. The corticofugal part is further subdivided into components that are categorized according to their connectivity pattern. To this end, cortico-rubro-spinal, cortico-rubro-cerebellar, cortico-reticulo-spinal, cortico-tecto-spinal, and cortico-vestibulo-spinal pathways have been identified as distinct functional units within the extrapyramidal mosaic [1, 10, 11, 17, 19, 20, 38, 44]. With regard to their macroscopic anatomy, it has been advocated by previous tractographic studies that the main bulk of the human descending extrapyramidal fibers converge toward a confined anatomical area within the internal capsule and form a wide corticotegmental system before reaching the brainstem [12, 17, 19, 30]. This fiber system can be therefore perceived as an extensive cortico-subcortical river that receives various extrapyramidal tributaries. A key anatomical observation in support of the structural relationship of the CTT to the extrapyramidal circuitry is that the fibers of this bundle were consistently recorded to connect the cortex with the tegmental area and cannot be allocated to any of the major sensory pathways passing through the tegmental area since these typically synapse in the thalamus [22, 29].

Among the most well-studied corticotegmental subcomponents is the corticoreticular tract (CRT). This pathway that allegedly participates in postural control and locomotor function has attracted special attention during the last decade. More specifically, Yeo and colleagues published the first DTI study which provides structural evidence on the anatomy of the human corticoreticular tract [43]. The authors succeeded in consistently identifying the CRT as a fascicle initially stemming from the premotor cortex (BA6) and precentral gyrus (BA4), projecting then medially and anterior to the CST and entering the tegmental area before terminating in the mesencephalic and pontine reticular formation. In a recent paper, Jang and Seo explored the cortical distribution of the CRT [18]. According to the authors, the tract was seen to originate predominantly from the primary motor and premotor cortex (100% of the hemispheres), with axons traced in the somatosensory cortex in 76.2% of cases. Later on, the same authors validated the subcortical distribution of the CRT in agreement with the pattern proposed by Yeo and colleagues [19].

Table 2 Distribution of corticotegmental fibers in tegmentum and ventral projection—anatomical zones

Zone	Anatomical location	Receives fibers from:	Projects fibers to (associated tract)
1a	Ventral-medial	BA 8 (SMA and FEF)	Medulla oblongata and spinal cord (reticulospinal and rubrospinal)
1b	Ventral-medial	BA8 (SMA and FEF)	Fibers decussate toward the contralateral tegmentum (decussation of superior cerebellar peduncle—cortico-rubro-cerebellar tract)
2	Ventral-middle	BA 8 (SMA and FEF)	Superior and inferior colliculi and medial floor of the 4th ventricle (corticotectal tract, corticomesencephalic tract and medial longitudinal fasciculus)
3	Ventral-lateral	BA 8 (SMA and FEF)	Superior peduncle and lateral floor of the 4th ventricle (corticocerebellar tracts)
4a	Medial-medial	BA4 and 6 (MC and PMC)	Medulla oblongata and spinal cord (reticulospinal and rubrospinal)
4b	Medial-medial	BA4 and 6 (MC and PMC)	Fibers decussate toward the contralateral tegmentum (decussation of superior cerebellar peduncle—cortico-rubro-cerebellar tract)
5	Medial-middle	BA4 and 6 (MC and PMC)	Superior and inferior colliculi and medial floor of the 4th ventricle (corticotectal tract, corticomesencephalic tract and medial longitudinal fasciculus)
6	Medial-lateral	BA4 and 6 (MC and PMC)	Superior peduncle and lateral floor of the 4th ventricle (corticocerebellar tracts)
7	Dorsal-medial	BA1/2/3 (SSC)	Medulla oblongata and spinal cord (reticulospinal and rubrospinal)
8	Dorsal-middle	BA1/2/3 (SSC)	Superior and inferior colliculi and medial floor of the 4th ventricle (corticotectal tract, corticomesencephalic tract and medial longitudinal fasciculus)
9	Dorsal-lateral	BA1/2/3 (SSC)	Superior peduncle and lateral floor of the 4th ventricle (corticocerebellar tracts)

BA Brodmann's area, *FEF* frontal eye fields, *MC* motor cortex, *PMC* premotor cortex, *SMA* supplementary motor area, *SSC* somatosensory cortex

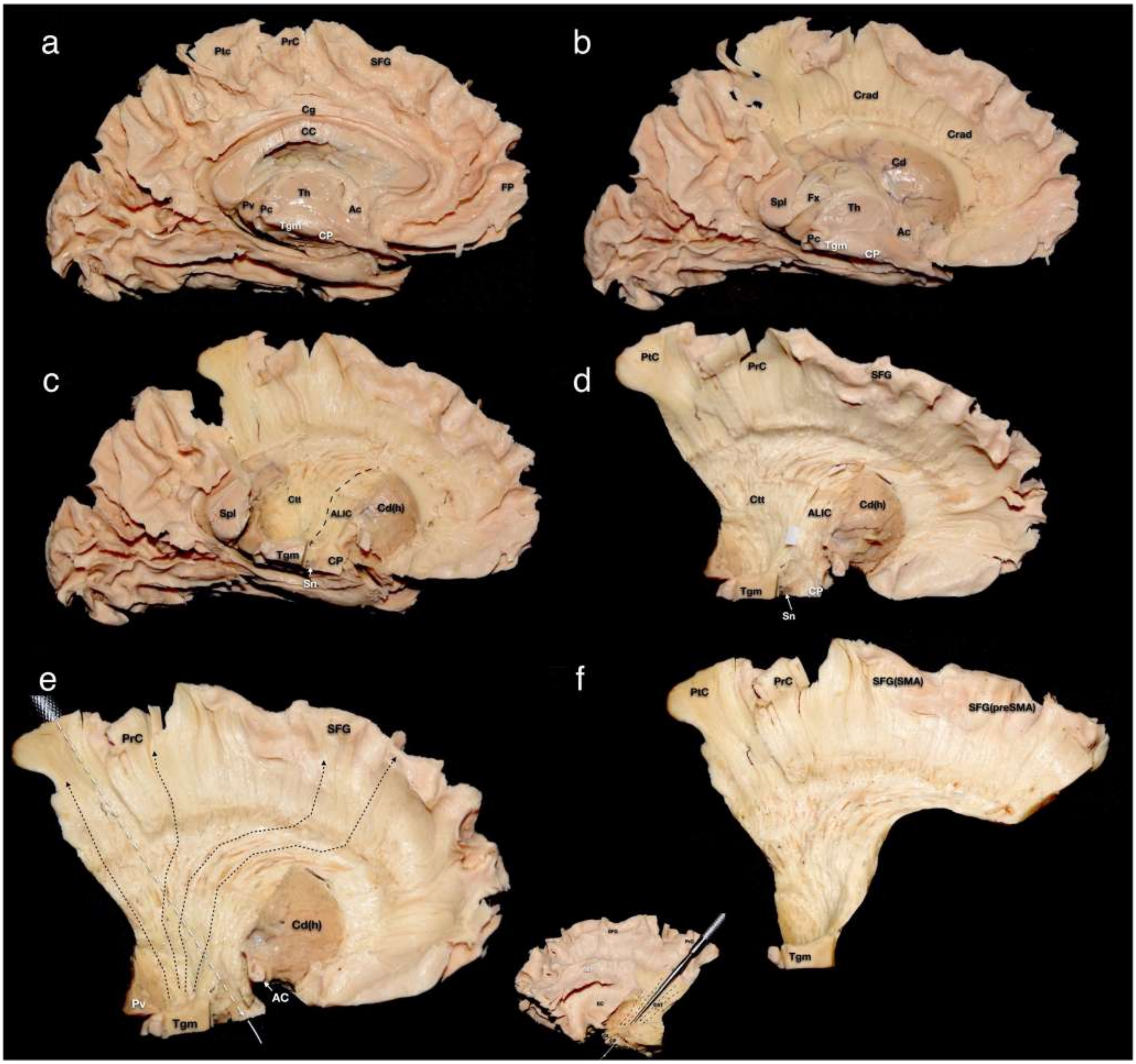

Fig. 1 Left hemisphere. Stages of a Medial to Lateral dissection. **a** Superficial U-fibers exposed. **b** Superior arm of the cingulum, corpus callosum, and superficial U-fibers removed. Callosal radiations are exposed. The anatomy of the lateral ventricle is illustrated. **c** The body and head of the caudate nucleus and the fibers of the thalamic radiations are removed. Fibers of the CTT can be seen at the level of the genu and posterior limb of the internal capsule, just posterior to the anterior limb of the internal capsule. **d** Posterior part of the hemisphere removed. CTT topography and morphology illustrated. **e** A dissector is used to resemble the trajectory of the fibers of the CST (Inset). The different orientation of the CTT and CST is illustrated. **f** CTT and superior tegmentum are dissected free from the rest of the hemisphere. Ac anterior commissure, ALIC anterior limb of the internal capsule, CC corpus callosum, Cd(h) head of the caudate nucleus, Cd caudate nucleus, Cg cingulum, CP cerebral peduncle, Crad callosal radiations, Ctt corticotegmental tract, EC external capsule, FP frontal pole, Fx Fornix, Ot optic tract, Pc posterior commissure, PrC precentral gyrus, Ptc postcentral gyrus, Pv pulvinar, SFG superior frontal gyrus, SLF superior longitudinal fasciculus, SMA supplementary motor area, Sn substantia nigra, Spl splenium, Tgm tegmentum, Th thalamus

The corticorubral projections in turn have been repeatedly investigated in the non-human primate brain. According to the seminal studies of Humphrey, Gold, and Reed, the red nucleus receives direct cortical input from areas BA4, BA6, BA8, and BA 5 [15, 16]. Nevertheless, very limited evidence exists on the related anatomy and connectivity of this tract in the human brain. Recent DTI studies support the existence of a corticorubral pathway connecting the superior frontal gyrus, superior aspect of the precentral and postcentral gyri, and paracentral lobule to the red nucleus [3, 12, 35]. According to these reports, the cortico-rubral fibers travel within the internal capsule before reaching their target.

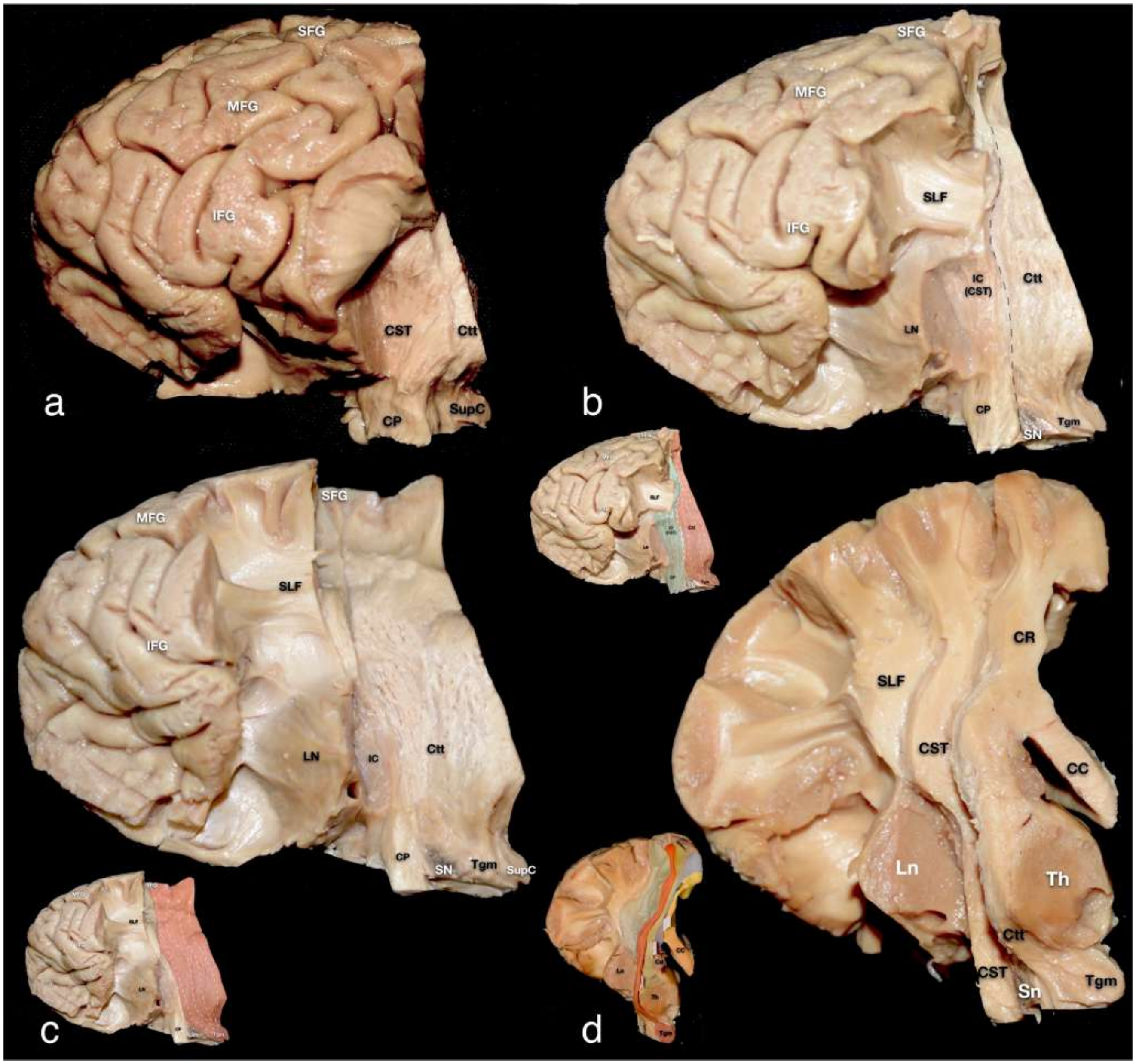

Fig. 2 Left hemisphere. Views of a multilayered lateral to medial dissection. **a** The corticospinal and corticotegmental tracts exposed at the level of the insula. The dissection process starts from the mesencephalic area and proceeds superiorly. CST fibers enter the cerebral peduncle while CTT fibers are seen to travel posterior to the substantia nigra entering the tegmental area. **b** SLF is revealed at the level of the middle frontal gyrus. At the level of the insula, the lentiform nucleus is exposed. CST and CTT fibers are further meticulously dissected, and their spatial relationship can be appreciated. Inset: CTT fibers are highlighted in red color and CST fibers in magenta. **c** Removing the corticospinal tract exposes the trajectory of CTT fibers more clearly. Inset: CTT fibers are highlighted in red. **d** Coronal view of the same hemisphere. The different white matter layers can be appreciated. Inset: Different colors are used for the fibers of the CST (magenta), CTT(red), thalamic radiations (green), frontocaudate tract (blue) and corpus callosum (yellow). Cd caudate nucleus, CP cerebral peduncle, CST corticospinal tract, Ctt corticotegmental tract, IC(CST) internal capsule (corticospinal tract), IFG Inferior frontal gyrus, Ln lentiform nucleus, MFG middle frontal gyrus, SFG superior frontal gyrus, SLF superior longitudinal fasciculus, Sn substantia nigra, SupC superior colliculus

Below the level of the red nucleus, the corticorubral fibers seem to be distributed along two descending pathways: the rubro-cerebellar pathway projecting to the ipsilateral and contralateral cerebellar hemisphere through the superior cerebellar peduncle and the rubro-spinal entering the lateral funiculus.

While the direct connectivity between the cortex, reticular formation, and red nucleus has been more or less documented,

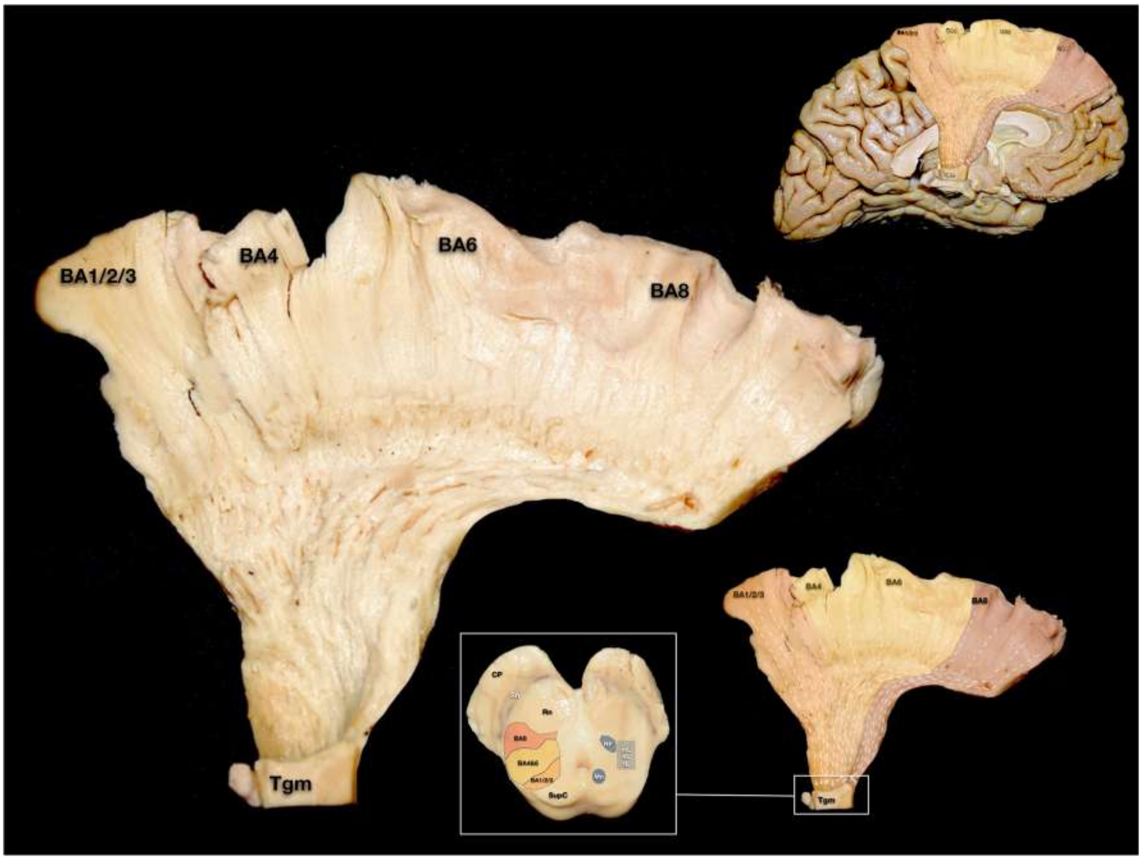

Fig. 3 Medial views of a left hemisphere showing the morphology, cortical terminations, and distribution pattern of CTT fibers in the tegmental entry zone. CTT fibers originate from the middle and posterior aspect of the superior frontal gyrus (BA6 and 8), precentral gyrus (BA4), postcentral gyrus (BA1/2/3), and paracentral lobule (BA4 and BA1/2/3) and exhibit an oblique fan-shaped configuration. Lower right inset: segmentation of the CTT according to cortical origins: anterior segment (red color) originates from BA8 (preSMA, DPFC, FEF), middle segment (yellow color) stems from BA4 and BA6 (DPMC and MC) and posterior segment (orange color) starts from BA1/2/3(SC). The trajectory of each component is marked with interrupted lines. Superior inset: the silhouette of CTT is superimposed on the medial surface anatomy. Lower left inset: the tegmental entry zone is illustrated. Different colors are used to highlight the distribution of fibers according to their cortical origin. The location of the mesencephalic reticular formation, medial lemniscus, spinal and trigeminal lemniscus, and mesencephalic nucleus are also illustrated. BA Brodmann's area, CP cerebral peduncle, mL medial lemniscus, Mn mesencephalic nucleus, RF reticular formation, Rn red nucleus, sL spinal lemniscus, Sn substantia nigra, Tgm tegmentum, tL trigeminal lemniscus

cortical projections to the tectum and oculomotor nuclei have only been advocated by studies in non-human primates. The term cortico-mesencephalic tract has been used by Levin in 1936 to describe projections from BA8 to the tegmental area. Forty years later, Astruc and colleagues validated the presence of relevant fibers that originate from BA8 and travel within the internal capsule toward the tegmental area, again in the brain of non-human primates [41]. However, the presence of a corticotectal or corticomesencephalic pathway involved in oculomotor function has not been adequately supported by relevant structural evidence in humans.

It can be well argued that tractographic studies have offered a crucial yet generic anatomical perspective of the various fiber tracts that contribute to the corticotegmental connectivity, and therefore, it is difficult to draw definite conclusions on the topography and architecture of the fibers of this system. It is for this reason that we opted to explore the structural characteristics of the descending extrapyramidal pathway through a direct anatomical method like the white matter fiber dissection technique, which is meticulously proven to provide data of high accuracy. Hence, our results reveal that the CTT can be consistently traced as a distinct white matter pathway traveling in the deep layer of the genu and posterior limb of the internal capsule. It is always located medial to the CST and exhibits a different fiber orientation, maintaining a clear but tight cleavage plane from the CST, which aids in their proper differentiation. In addition, we were able to systematically map the cortical termination pattern of the CTT. This area includes the superior aspect of motor, premotor, dorsal prefrontal and somatosensory cortices and coincides with the cortical origin of the various extrapyramidal tracts as illustrated by previous tractographic studies. The observed percentage of terminations to the somatosensory cortex (present in 13/20 of the studied specimens) may be indicative of the fact that the CTT's anterior and middle segments are thicker and bulkier than the

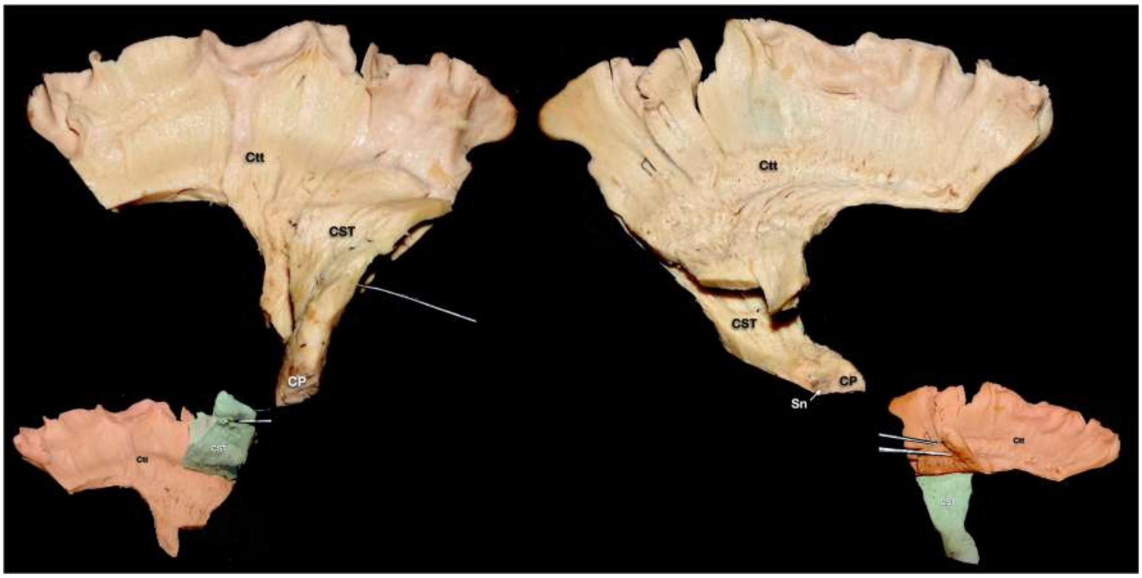

Fig. 4 Lateral (left side of the photo) and medial views (right side of the photo) of an advanced dissection stage of a left-sided specimen. The spatial relationships of the CTT and CST are shown. CTT incorporates fibers originating from a wider cortical area compared with the CST. CST travels anterior to the substantia nigra in contrast to CTT fibers that follow a more posterior trajectory. The different orientation of the two fiber systems can be appreciated. These two fiber tracts can be adequately dissected and differentiated in all studied hemispheres. CP cerebral peduncle, CST corticospinal tract, Ctt corticotegmental tract, Sn substantia nigra

posterior segment (see "Results" section). As such, the relatively fewer fibers that terminate toward the BA1/2/3 may be difficult to track, identify, and categorize due to the limitations of the fiber dissection technique.

We further went on and tried to parcellate these fibers according to their corresponding cortical—and therefore functional—origin. As analyzed in the "Results" section, the fibers originating from BA8, BA4/6, and BA1/2/3 share an anteroposterior spatial orientation. Hence, the CTT can be perceived as a fiber tract composed of 3 distinct anatomo-functional segments: an anterior segment stemming from the pre-SMA/FEF/DPMC, a middle segment descending from the DPMC and PMC, and a posterior segment carrying fibers from the SC. In a step further, we meticulously defined the infra-tegmental distribution of these fibers among various descending pathways projecting to the tectal area (corticotectal pathway, corticomesencephalic pathway), superior cerebellar peduncle (cortico-rubro-cerebellar pathway), floor of the fourth ventricle (projections to locus coeruleus, vestibular nuclei and oculomotor nuclei), and tegmento-spinal connections toward the anterior(anterior reticulo-spinal) and lateral (lateral reticulo-spinal and rubro-spinal tracts) funiculus (see Table 2).

The results of this study lend support to the hypothesis that the CTT serves primarily as an extrapyramidal "conduit," although it cannot be excluded that fibers conveying different functions are also included. As such, the CTT allegedly represents a carrier of multimodal cues related to locomotion, postural control, tone adjustment, motor inhibition, organization of complex movements, and reflex control.

Toward a dynamic, hodotopical, and delocalized model for motor behavior: anatomo-functional substrates and clinical repercussions

In neurosurgery, the corticospinal and corticobulbar tracts have attracted special interest and have been extensively studied as key components for the preservation of motor function. In this vein and mainly driven by the advent of awake brain mapping techniques, numerous studies have offered important online data with regard to the function and neural correlates of the pyramidal circuitry by means of MEPs, direct cortical stimulation of the primary motor cortex, and subcortical stimulation of the corticospinal fibers [6, 7, 13, 27, 31, 39]. Further and in the same context, tractographic representations of the CST's topography have also been used in intraoperative neuronavigation systems during image-guided neurosurgical procedures as a method to preserve the primary motor circuit and to correlate anatomical, functional, and radiological data [9, 21, 32, 34]. Nonetheless, the same spirit did not apply for the extrapyramidal component of the human motor network mainly because its structural architecture was for a long period ill defined.

However, a paradigm-shift is emerging. Our perception of the neural correlates of fine motor behaviors has significantly changed primarily due to the results of awake brain mapping studies in combination with novel structural data stemming from white matter dissection and tractographic techniques [8, 36, 37]. In essence, the role and relationship

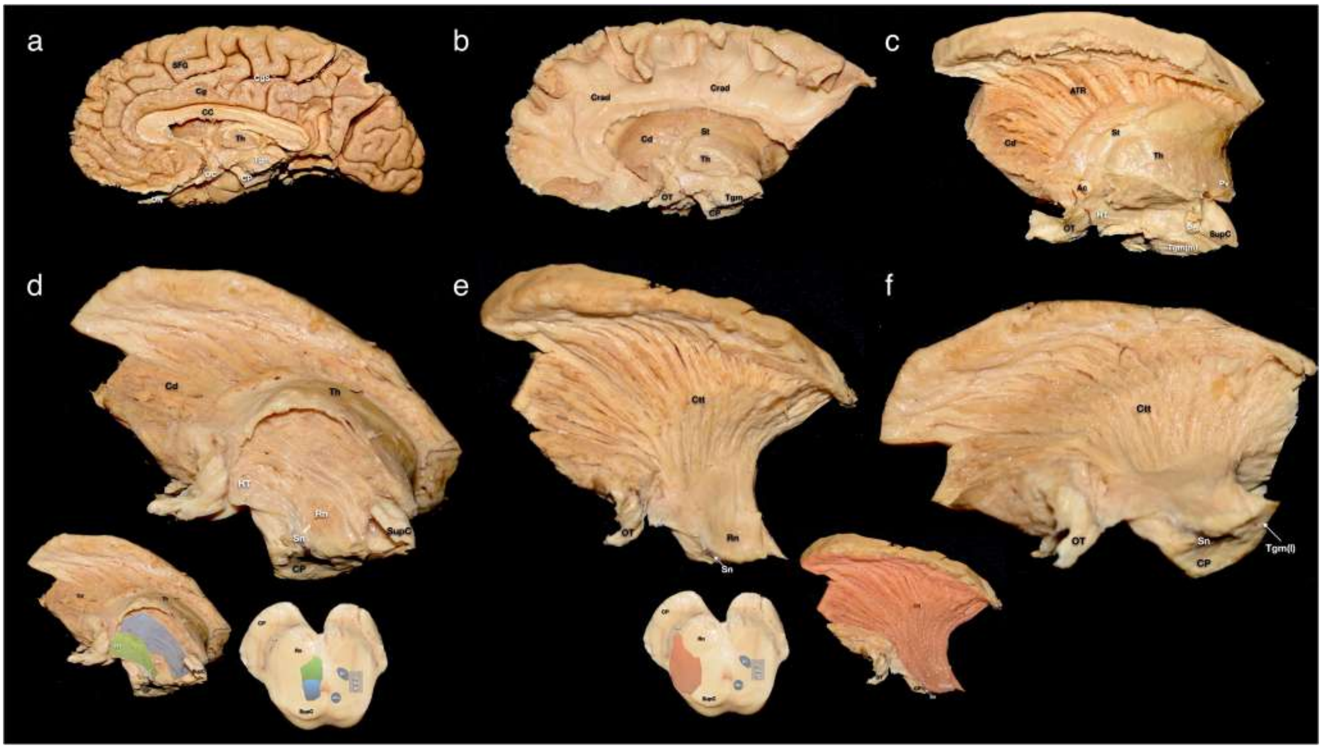

Fig. 5 Medial views of a progressive nuanced dissection of a right hemisphere. The ventral allocation of CTT fibers and their relationships to diencephalic structures, thalamic radiations, and thalamo/hypothalamotegmental fibers are shown. **a** Medial aspect of the hemisphere and corresponding surface anatomy. **b** The cortical grey matter, superficial U-fibers, and superior arm of the cingulum have been removed exposing the callosal radiations. **c** The central core and mesencephalon are dissected free from the rest of the hemisphere. Removing the grey matter of the caudate nucleus reveals the anterior thalamic radiation (ATR). ATR fibers are seen to bypass the caudate and reach the thalamus at the area of the stria terminalis. Gradual dissection of the ATR exposes the frontocaudate tract (FCT) as it terminates in the superolateral aspect of the caudate nucleus. **d** The medial aspect of the thalamus and hypothalamus is dissected to reveal the thalamo- and hypothalamotegmental fibers that project toward the medial aspect of the tegmentum. Inset (left): the thalamotegmental and hypothalamotegmental fibers are highlighted in blue and green color respectively. Inset (right): the entry zone of the thalamotegmental and hypothalamotegmental fibers at the superior tegmentum (level of the superior colliculi) is highlighted in blue and green respectively. **e** Dissecting away the fibers of the ATR and the grey matter of the caudate nucleus uncovers the CTT. Its fibers travel posterior to the substantia nigra and enter the lateral aspect of the tegmentum. Inset (left): The TEZ of the CTT is highlighted in red color. Inset (right): CTT is highlighted in red color. **f**: Inferomedial view of the same specimen. CTT fibers can be seen reaching the tegmentum at its lateral half. Ac anterior commissure, ATR anterior thalamic radiation, CC corpus callosum, Cd caudate nucleus, Cg cingulate gyrus, CgS cingulate sulcus, CP cerebral peduncle, Crad callosal radiations, HT hypothalamus, mL medial lemniscus, Mn mesencephalic nucleus, OC optic chiasm, ON optic nerve, OT optic tract, Pc posterior commissure, Pv pulvinar, RF reticular formation, Rn red nucleus, SFG superior frontal gyrus, sL spinal lemniscus, Sn substantia nigra, St stria terminalis, Tgm(l) lateral tegmental area, Tgm(m) medial tegmental area, Tgm tegmentum, Th thalamus, tL trigeminal lemniscus

of the human pyramidal and extrapyramidal systems in motor organization and execution have been reassessed in the light of converging anatomo-functional evidence focusing on extrapyramidal pathways like the frontocaudate tract, the frontostriatal pathway, the frontal aslant tract, the frontal longitudinal system etc. and pave the way toward a parallel, delocalized, and dynamic model for motor behavior [2, 23, 25, 26].

To this end, clarifying the anatomical architecture of the extrapyramidal system is crucial to the development of methods aiming to map and further appreciate the role of this network in programming and execution of movement. The present endeavor is one of the limited studies offering sound structural evidence on the morphological characteristics of the descending human extrapyramidal pathway that could be employed intraoperatively to assess its function and clinical significance. Future studies are definitely needed to further link the spatial structural distribution with the functional sub-specialization of the human extrapyramidal pathways.

Study strengths and limitations

The white matter dissection technique entails the fixation of cerebral hemispheres in a formalin solution followed by a freeze/thaw procedure [24]. This method has been microscopically proven to preserve the integrity and structure of the white matter fibers while interfering exclusively with the extracellular matrix, and therefore, the results obtained on the morphology and topography of the white matter pathways are of high sensitivity and accuracy [45]. Due to these reasons and

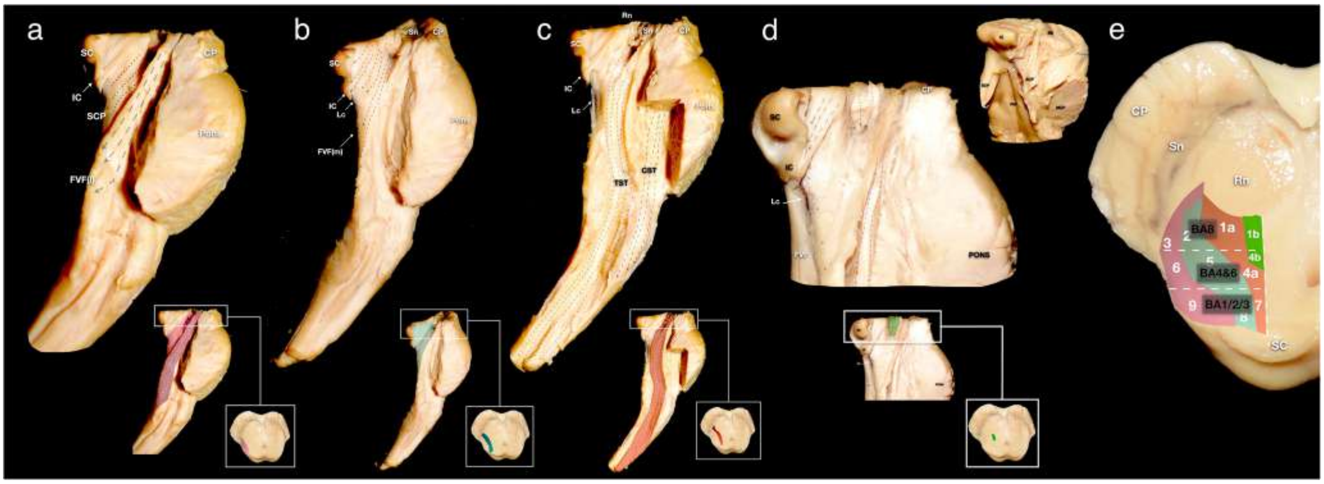

Fig. 6 Lateral to medial dissection of the brainstem below the level of the superior colliculi. **a** Lateral view. In the first and most superficial layer, the bulk of the fibers projects toward the superior cerebellar peduncle and the lateral part of the 4th ventricle floor. These fibers maintain an orientation of approximately 45°. Inset: Fibers projecting to the superior cerebellar peduncle and to lateral aspect of the floor of the 4th ventricle are highlighted in light and dark pink respectively. The distribution of these fibers at the level of the TEZ is highlighted in pink in the axial plane. **b** Lateral view. The second consecutive layer of fibers can be seen to project toward the tectal area (superior and inferior colliculus) and the superior part of the 4th ventricular floor (area of the locus coeruleus). These fibers exhibit a more horizontal configuration of approximately 30–40°. Inset: Fibers projecting to the tectal area and superior aspect of the floor of the 4th ventricle are highlighted in light and dark magenta respectively. The distribution of these fibers at the level of the TEZ in the axial plane is highlighted in magenta. **c** The 3rd consecutive layer mainly consists of longitudinal descending fibers that project in a 90° angle toward the lateral and anterior funiculus. These fibers travel at the same plane but posterior to the pyramidal fibers. Inset: The longitudinal fibers projecting to the lower brainstem and spinal cord are highlighted in red color. The distribution of these fibers at the level of the TEZ in the axial plane is highlighted in red. **d** The 4th and deepest fiber layer can be seen to project from the superior cerebellar peduncle and red nucleus and contributes to the ventral tegmental decussation. These fibers take a 45° orientation toward the contralateral tegmental area. Inset (lower): Fibers projecting toward the ventral tegmental decussation are highlighted in green. The distribution of these fibers at the level of the TEZ is highlighted in green. Inset (upper): Posterolateral view of a different specimen. The fibers originating from the superior cerebellar peduncle can be followed toward the ventral tegmental decussation. The more superficial fibers projecting to the tectum and locus coeruleus can be also appreciated. **e** Axial cut of the tegmentum at the level of the superior colliculi. Left side. The aforementioned layers are superimposed on the TEZ. In this way, a diagram matching the respective cortical origins of the CTT fibers to possible projection areas below the level of the superior colliculus is created. This diagram includes 11 different zones that are summarized in Table 2. The same corresponding colors are used to illustrate the four subsequent layers of infrategmental fibers with respect to their cortical projection from Brodmann's areas 1, 2, 3, 4, 6, and 8. CP cerebral peduncle, CST corticospinal tract, FVF(l) lateral aspect of the 4th ventricle floor, FVF(m) medial aspect of the 4th ventricle floor, FVF floor of the 4th ventricle, IC inferior colliculus, Lc locus coeruleus, MCP middle cerebellar peduncle, Rn red nucleus, SC superior colliculus, SCP superior cerebellar peduncle, Sn substantia nigra, TST tegmentospinal tracts

because this is a direct anatomical method of data acquisition, it stands as one of the "gold standard" techniques used to validate data deriving from DWI-based tractography, as the latter is documented to suffer from inherent limitations particularly when kissing, bending, and crossing fiber populations are explored [40]. Compared with traditional histology and optical coherence tomography, the white matter dissection technique maintains the three-dimensional coherence of the fiber tracts, thus providing a better spatial perception of the subcortical architecture.

Nonetheless, the fiber dissection technique is a time-consuming process that heavily relies on the experience and the technical skills of the operator. In addition, the spatial resolution is lower when compared with histology and optical coherence tomography [4, 28]. This is an important caveat when studying fiber tracts that participate in the brainstem connectivity, as the sensitivity of the fiber dissection is limited in detecting termination patterns in this complex area. However, in the case of the CTT, our aim was to address the macroscopic anatomy of the tract and provide a three-dimensional understanding of its related topography and morphology. Finally, we tried to tackle this shortcoming by using the "origin to projection of fibers" technique (Figs. 1, 2, 3, 4, 5, 6, and 7; Table 2) as described in the "Results" section.

Conclusion

Using the fiber microdissection technique, we were able to readily identify the corticotegmental tract (CTT) as a group of fibers connecting the frontal and parietal cortex to the tegmental area. The fibers of the CTT are putatively assigned to the descending component of the extrapyramidal pathway and are allegedly implicated in complex motor behavior. In the current study, the intrahemispheric architecture, morphology, and correlative anatomy of the CTT are elucidated for the first time in the current

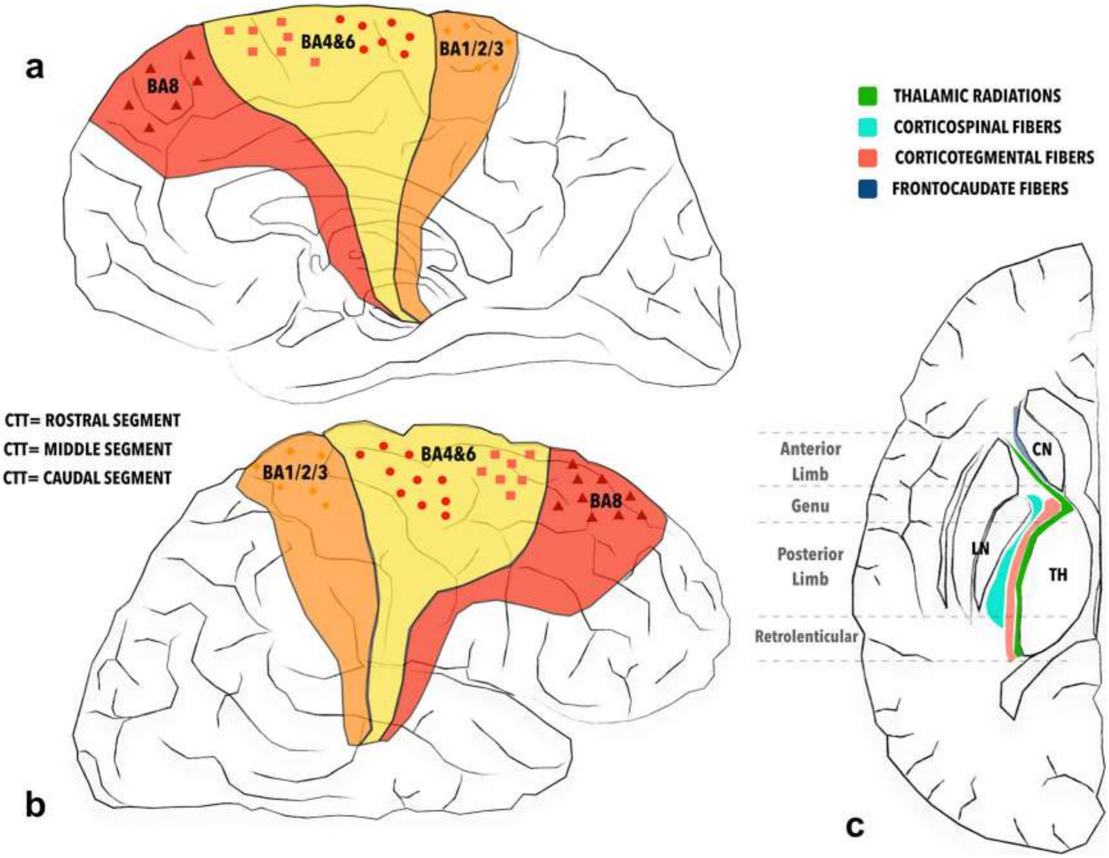

Fig. 7 **a**, **b** Medial (**a**) and lateral (**b**) schematic representations of a right hemisphere. The morphology and trajectory of the fibers of the CTT are illustrated. The rostral, middle, and caudal segments of the tract are highlighted in red, yellow, and orange color, respectively, and superimposed on a schematic drawing of the hemisphere. The diamonds, circles, squares, and triangles represent the areas of cortical termination of the corticotegmental fibers in Brodmann's areas 1/2/3(somatosensory cortex), 4, 6, and 8, respectively. **c** Schematic representation of an axial cut of a cerebral hemisphere at the level of the basal ganglia, thalamus, and internal capsule. The topography of the CTT with respect to the adjacent fiber tracts is illustrated. The segments of the internal capsule (i.e., anterior limb, genu, posterior limb, retrolenticular part) are exhibited. The corticotegmental fibers, corticospinal fibers, thalamic radiations, and frontocaudate fibers are highlighted in red, cyan, green, and dark blue color, respectively. CTT mainly travels in the genu, posterior limb, and retrolenticular part of the internal capsule medial to the fibers of the corticospinal tract while the thalamic radiations and frontocaudate fibers extend to the anterior limb of the internal capsule. CN caudate nucleus, CTT corticotegmental tract, LN lentiform nucleus, TH thalamus

literature. Our results provide sound structural evidence on the anatomy of the descending extrapyramidal system and at the same time offer anatomical information that can be integrated in the preoperative and intraoperative planning in neuro-oncological cases. Definitely, further studies focusing on the CTT structure to function relationship are needed to provide a comprehensive understanding of the clinical repercussions of this fiber tract.

Code availability Not applicable

Authors' contribution Conception and design: Komaitis, Koutsarnakis. Acquisition of data: Komaitis, Koutsarnakis, Liakos, Kalyvas, Gerogiannis, Drosos, Skandalakis, Neromyliotis. Analysis and interpretation of data: Komaitis, Koutsarnakis, Kalyvas, Liakos. Drafting the article: Koutsarnakis, Komaitis. Critically revising the article: Koutsarnakis, Stranjalis, Troupis, Komaitis. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Koutsarnakis. Administrative/technical/material support: Stranjalis. Study supervision: Koutsarnakis

Data Availability Not applicable

Declarations

Ethics approval This study was approved by the Bioethical Committee of the Medical School of the National and Kapodistrian University of Athens (Reference number: 118 Issue date: 21/05/2019).

Informed consent This is a cadaveric study not involving patients or patient related information. All cadaveric specimens used in the current study were obtained by the providing company after strict self-consent or consent from the legally authorized representatives or next of kin of the donors.

Consent for publication Not applicable

Conflict of interest The authors declare that they have no conflict of interest.

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