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1 The pathophysiology of motor thalamus

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Abstract

The thalamus is considered an important structure of sensitive pathways, and also intervenes in motor tasks. It receives multiple cortical and subcortical afferent fibers and the relations between their different nuclei are intense. After anatomic and functional study of the thalamic structure and its connections, we will analyze the different classifications and proposed subdivisions of the thalamic nuclear groups both in primates and humans. We will direct our study towards those aspects of the thalamus related to movement. The motor thalamus is described in most non-human primate studies as the thalamic region that receives

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subcortical afferent fibers from the basal ganglia and the cerebellum, and cortical fibers of the primary motor and pre-motor areas and these functions are also inferred to the human thalamus based on the cytoarchitectonic similarity between them.

Later on, the pathological clinical aspects related to the motor thalamus are discussed. Disturbances or impairments in the coordination and course of movement, in muscular tone, and movement planning can be associated with injuries located in the motor thalamus and its connections. The research related to surgical procedures involving the thalamic structure for the treatment of impairments or disturbances of motion and movement are examined and will permit a comprehensive summary of the different mechanisms involved in the pathophysiology of the motor thalamus.

Introduction

The term *"thalamus"* derives from the Greek word *"thalamos"* which means *"internal chamber" or "nuptial bedroom"*. Embryologically it develops from the diencephalic vesicle, which also derives from the prosencephalic vesicle. After both telencephalata have been formed, a central zone is delimited from which the future diencephalon will develop.

The thalamus is oval in shape with a more or less symmetrical structure in relation to its mid-line. The human thalamus is about 3 cm in length (anteroposterior) and 1.5 cm wide at its widest point [1]. Each thalamic ovoid is crossed by a myelinic fiber band, the *internal medullar lamina*, which runs throughout the rostrum-caudal extension, adopting a special distribution shaped like a "Y" in the anterior pole and dividing the thalamus into large anatomic functional blocks. This lamina contains intrathalamic fibers that connect the different nuclei of the thalamus. Another band, the *external medullar lamina*, forms the lateral boundary of the thalamus, medial to the internal capsule. It contains nervous fibers that leave or enter the thalamus on their path towards or from the adjacent capsule.

In each ovoid we can differentiate four surfaces or faces: medial, lateral, superior and inferior; and two poles: anterior and posterior. The *medial face* of the thalamus serves as a limit to the III ventricle and each ovoid contributes to form the superior half of the wall of this cavity. This medial face is in contact with the cerebrospinal fluid. The medial faces of both thalami are attached to each other by interthalamic fibers known as *intermediate mass, interthalamic adherence* or *gray interthalamic commissure*. The concave shaped *lateral face* is separated from the lenticular nucleus by the posterior arm of the internal capsule. The *superior face* of the thalamus is divided by a sulcus, called choroid groove, in an internal portion, in contact with the body of the fornix, and the external part of the base of the central portion of the corresponding lateral ventricle, in which the choroid plexuses are situated. The *inferior face* is

anatomically related to the lateral subthalamic nuclei and the medial hypothalamus. The *anterior pole of the thalamus*, along with the anterior pillar of the fornix, delimits the interventricular Monro's foramina. In the inferior-posterior zone, the thalamus borders on the mesencephalon.

The thalamus, along with the cerebral cortex, plays an important role in the analysis and integration of the sensory and motor functions. All sensorial information, except the sense of smell, goes through the thalamus to project to the corresponding specific cortical areas. The participation of the thalamus in motor control is reflected by the afferent fibers coming from the basal ganglia, cerebellum and motor cortex and the efferent fibers towards the motor and pre-motor cortex. In addition to its implication in sensory and motor functions, the thalamus participates in higher functions, such as attention, language, memory and the executive function.

Thalamic nuclear groups

The thalamus contains a very rich nuclear organization. The thalamic nuclei nomenclature is very complex and in some cases their connections are not well known [2]. Several classifications of the different nuclei that make up the thalamus have been proposed based on their location with respect to the internal medullar lamina, the function they carry out and their connections, etc.

From an evolutionary perspective Elliot [3] divided the thalamic nuclei phylogenetically into three groups: 1 - *Archithalamus* (nuclei of the mid-line; intralaminar and reticular). 2 - *Paleothalamus* (geniculated bodies; posterior ventral nuclei; cerebellar and anterior). 3 - *Neothalamus* (medial nuclei; laterodorsal; lateral posterior and ventral anterior).

Morel et al. [4] have proposed a classification considering the cytoarchitectonic criteria described in humans and non-human primates and the nomenclature generally used in monkeys was adapted to the human thalamus by Hirais and Jones [5]. According to this criterion the human thalamus is divided into the following nuclear groups: 1 - lateral; 2 - medial; 3 - posterior; 4 - anterior; and 5 - reticular nuclei (see table 1).

Finally, considering anatomo-functional aspects, seven nuclear groups are recognized: 1 - anterior, 2 - dorsomedial, 3 - lateral, 4 - posterior, 5 - nuclei of the medium line, 6 - intralaminar nuclei and 7 - reticular nuclei (see table 2).

1 - The *anterior nuclear group* is located in the anterior thalamic pole, in the deployment of the internal medullary lamina. It consists of a large main nucleus, the *anteroventral* (AV), and *anterodorsal* nuclei (AD) and the *anteromedial* (AM), (table 2). The anterior nuclear group of the thalamus is part of the limbic system, which is related to emotional conduct and mechanisms of learning and memory.

2 - The *dorsomedial nucleus* (DM) occupies most of the area located between the internal medullar lamina and the periventricular gray substance. It

Table 1. Classification of the thalamic nuclei based on cytoarchitectonic criteria.

Nuclear group	**Main nuclei**
Lateral	*Ventroposterior Complex* - Ventral postero-lateral nucleus - Ventral postero-medial nucleus - Ventral postero-inferior nucleus *Ventral lateral nucleus:* - Ventral lateral posterior nucleus - Ventral lateral anterior nucleus *Ventral anterior nucleus* *Ventral medial nucleus*
Medial	*Intralaminar Nuclei:* - Central medial - Parafascicular - Central lateral *Dorsomedial nucleus:* - Dorsomedial paralaminar - Dorsomedial parvocellular - Dorsomedial magnocellular - Midline nuclear group
Posterior	*Posterior Complex:* - Limitant nucleus - Suprageniculate nucleus - Posterior nucleus *Lateral posterior nucleus* *Pulvinar* *Geniculate Nucleus:* - Lateral - Medial
Anterior	*Anteroventral nucleus* *Anteromedial nucleus* *Anterodorsal nucleus* *Lateral dorsal nucleus*
Reticular Nuclei	

extends medially throughout 2/3 of the anteroposterior length of the thalamus. The DM nucleus is most developed in human beings. In non-primates three portions can be distinguished: a central, medial and lateral portion. The central portion is the only one related to olfactory areas of the cerebral cortex. The medial portion has connections and it is functionally related to diverse structures of the vegetative nervous system and the limbic system (amygdala). The functions of the lateral portion are not well known; it is thought that it may participate in the control of eye and head movements, in relation to attention mechanisms. In primates and human beings three main cytoarchitectonic regions

Table 2. Classification of the thalamic nuclei based on anatomofunctional criteria.

Nuclear Group	Main nuclei	Nomenclature
1- Anterior	*Anteroventral nucleus*	*AV*
	Anterodorsal nucleus	*AD*
	Anteromedial nucleus	*AM*
2- Dorsomedial	*Dorsomedial magnocellular*	*DMmc*
	Dorsomedial parvocellular	*DMpc*
	Dorsomedial paralaminar	*DMpl*
3- Lateral	*Dorsal zone:*	
	- Dorsolateral nucleus	- DL
	- Lateral posterior nucleus	- PL
	Ventral zone:	
	- Ventral anterior nucleus:	- VA:
	-- Parvocellular	--VApc
	-- Magnocellular	-VAmc
	- Ventral lateral nucleus:	- VL:
	-- Oral portion	--VLo
	-- Caudal portion	--VLc
	- Ventral posterior nucleus or ventrobasal complex:	- VP:
	-- Ventral posterolateral nucleus	--VPL
	-- Ventral posteromedial nucleus	--VPM
4- Posterior	*Pulvinar*	
	Geniculate medial	*CGM*
	Geniculate lateral	*CGL*
5- Mid line	*Paratenial nucleus*	
	Paraventricular nucleus	
	Reuniens nucleus	
	Romboid nucleus	
6- Intralaminar	*Centremedian nucleus*	
	Parafascicular nucleus	
	Paracentral nucleus	
	Central lateral nucleus	
	Central medial nucleus	
7- Reticular	*Reticular nucleus*	
	Mid line reticular nuclei	
	Centro median nucleus	

have been identified: - the *magnocellular* region (DMmc), in the dorsomedial and rostral portion the *parvocellular* region (DMpc), in the caudal position and the *paralaminar* region (DMpl), which forms an adjacent band to the internal medullar lamina. Two great functional parts can be differentiated in the DM, one motor (DMpl) and of the other limbic (DMmc and DMpc).

3 - The *Lateral nuclear group* is divided into dorsal and ventral zones.

The **dorsal or superior zone** consists of: the *dorsolateral nucleus* (DL) and the *posterior lateral nucleus* (PL). The DL nucleus extends throughout the inferior edge of the internal medullar lamina and is surrounded by a myelinic fiber capsule, similar to that of the anterior nuclear group. From an anatomical point of view this nucleus belongs to the dorsal group. Nevertheless, functionally it is part of the anterior group, with which it forms the limbic thalamus. The PL nucleus is located between the DL nucleus and the pulvinar. The limits between the LP and the pulvinar are not very clear so it is usually called the *pulvinar-lateral posterior complex* [6] and it is considered a nucleus of sensorial association in charge of the integration of diverse sensorial information.

The **ventral or inferior zone** includes the following nuclei: *ventral anterior (VA)*; *ventral lateral* (VL); *ventral posterior or ventrobasal complex* (VP). The VA nucleus is located on the rostral part of the ventral nuclear group, limited in an anterior and ventrolateral direction by the reticular nucleus. From a histological point of view the two parts can be identified: *parvocellular* (VApc) and *magnocellular* (VAmc).

The VA nucleus is involved in the planning of movements and constitutes an important station in the motor pathways from the basal ganglia to the cerebral cortex. Therefore it participates in the regulation of movements. The medial part (magnocellular) of VA is related to the control of the voluntary movements of the eyes, the head and the neck. The lateral part (parvocellular) participates in the control of movements of the body and extremities.

The VL nucleus is caudally located in relation to the VA. It is the main thalamic station of cerebellum projections with origins in the deep nuclei. It divides into an *oral part (pars oralis,* VLo*)* and a *caudal part (pars caudalis,* VLc*)*. It participates in the decoding of sensory stimuli that provide space information for moving objects. VA and VL constitute an important station in the motor system that connects the cerebellum, the basal ganglia and the cerebral cortex. Deep cerebellum nuclei usually project to the VL and from the pallidum to VA.

The VP nucleus is located in the caudal part of the thalamus, within two important nuclei: *ventral posterolateral* (VPL) and *ventral posteromedial* (VPM). The VPL also constitutes the station for fibers of the medial lemnisco and the spino-thalamic fiber, with sensory information from the trunk and extremities. This lateral portion is in turn divided into an *oral part (pars oralis* VPLo*)*, characterized by the presence of big cells, and a caudal part *(pars caudalis* VPLc*)* with the presence of big cells and a great density of small cells. The VPM, classically known as the arcuato or semilunar nucleus, is in a medial position with respect to the VPL nucleus. It consists of a main part composed of small and great cells called *ventro posteromedial*. It receives

somatic afferents from the face and intra-oral structure receptors, and has a part called *parvocelullar* (VPMpc) hat is related to taste.

4 - The *Posterior nuclear group*. is composed of the *pulvinar*, the *geniculated medial body* (CGM) and the *geniculated lateral body* (CGL). Pulvinar (from the Latin pulvinar, meaning "cushion") is a large nuclear mass that comprises posterior and dorsolateral sections of the thalamus and extends over the geniculated bodies and the dorsal surface of the mesencephalon. This nucleus has its maximum expression in the brain of primates, particularly in the human brain, and its development seems to be parallel to the growth of the association areas of the parieto-temporo-occipital cortex [7].

The CGM is located on the ventral caudal face of the thalamus, medial with respect to the CGL and dorsal to the cerebral peduncles. It is composed of three regions: ventral, dorsal and medial. The ventral region has a laminar structure and receives tonotopically-organized afferents from the central nucleus of the inferior cuadrigemic tubercle. Both divisions lack clear laminar structure.

The CGL is located in the lateral part with respect to the CGM and ventral to the pulvinar. This nucleus has a six layer laminated structure, the four dorsal parvocellular layers (3 to 6), formed by small size neurons, and two more ventral magnocellular layers, (1 and 2). The parvocellular layers receive axons coming from the retina and are fundamentally related to color perception, whereas the magnocellular layers receive the axons of the retina most sensitive to the changes in contrast and stimuli movement.

5 - *Mid-line nuclei*. These are not highly developed in human beings and are difficult to delimit, located in the periventricular gray substance, over the hypothalamic groove. They maintain close relations with the hypothalamus, intralaminar nuclei and dorsomedial nucleus. Within this group the *paratenial*, *paraventricular*, *reuniens* and *rhomboid nucleus* should be emphasized. They participate in the emotional, memory and autonomic functions.

6 - *Intralaminar nuclei*. They constitute a numerous series of neuronal cumuli located in the thickness of the internal medullar lamina of the thalamus. In human beings the two main bodies, from a functional point of view, are the *centermedian* and *parafascicular*. Other nuclei that are located more towards the rostral region include the *paracentral*, the *central lateral* and *central medial*. The intralaminar nuclei influence the cortical activity through other thalamic nuclei. They perform a global arousal function, due to their extrathalamic and cortical connections, and a specific function. The connections that these nuclei maintain with the putamen and the caudate nucleus contribute to subcortical motor control.

7 - *Reticular nuclei*. They cover the anterior pole and the lateral face of the thalamus, from which they are separated by the external medullar lamina. They are located between the external medullar lamina and the internal capsule. Of

these nuclei we wish to emphasize the *reticular nucleus* (thin lamina of gray vertical substance, that leans on the external face of the thalamus), the *reticular nuclei of the mean line* (small gray masses near the medial face of the thalamus) and the *center medium nucleus* (large nucleus located in the thickness of the external medullar lamina).

The intralaminar, reticular, and mean line nuclei, usually considered unspecific, are related to waking up, motor control and the awareness of sensorial experiences. Based on the connections, two great thalamic nuclear groups can be identified: specific and unspecific.

1. The *specific nuclei* have a specific and selective relation with a particular part of the neocortex. That is to say, they are intermediate links in the processing of information up to the cortex and they work in a complex way, collaborating in integration, selection, processing and transmission towards the cerebral cortex. Each of these nuclei receives projections from the area of the cerebral cortex to which it first sends efferents, creating a selective relationship with a particular portion of the neocortex. They are also known as cortical-dependent nuclei. Within these specific nuclei two types can be recognized: *specific nuclei of relay* and *specific nuclei of association*.

The *specific relay neurons* receive direct afferents from the subcortical areas and project to layer IV of the cerebral cortex. This group includes the following nuclei: anterior nuclear group, VA nucleus, VL nucleus, VP, CGL and CGM. For Martin [8], the relay nuclei are essential for all cerebral functions and each one plays a different role in perception, volition or cognition, transmitting information from particular subcortical structures to a limited portion of cortex.

The *specific association nuclei* receive cortical and other thalamic nuclei afferents and also project to diverse cortical layers (I, III and VI). This group includes the following nuclei: DL, LP, DM and pulvinar.

2. *Nonspecific nuclei* project to several cortical and subcortical regions. They are the mid line, intralaminar and reticular nuclei. For these nuclei the cerebral cortex is not the main zone of projection. It has been verified that both mid line and intralaminar nuclei send their projections to precise subcortical regions, so they seem not to be as unspecific as once thought [2]. They act when waking up and regulate the excitability of the biggest regions of the cerebral cortex [8]. They are also called cortico-independent nuclei.

From a functional point of view the thalamic nuclei are classified in:

1. *Motor*: they receive motor afferents from the basal ganglia (VA) and the cerebellum (VL) and they project to the premotor and primary motor cortices.
2. *Sensory*: they receive afferents from the somatosensorial ascending systems (VPL and VPM), auditory (CGM) and visual (CGL).

3. *Limbic*: they are related to limbic structures (mammilary bodies, hippocampus, cingulated gyrus).
4. *Associative*: they do not receive direct afferents from the long ascendant paths and project to association areas in the frontal, parietal and temporary lobes. They include the DM and the posterior pulvinar-lateral nuclear complex. They have the following characteristics in common: a) they do not receive afferents from the long ascending paths; b) most of their afferents come from other thalamic nuclei and c) their main projection goes to the association areas of the cerebral cortex.
5. *Unspecific and reticular*: they are characterized by diffuse and wide indirect cortical projections and by afferents from the reticular troncoencephalic formation. They include the intralaminar, mean line and reticular nuclei.

Main connections of the thalamic nuclei

In this section we will indicate the main afferents that arrive at the different thalamic nuclei and the efferents that come from them. For this purpose we will use the anatomo-functional classification proposed in the previous section.

1. The *Anterior nuclear group*. The main afferents to this nuclear group come from the hypothalamus (mammilary bodies) and the hippocampus formation. The mammilo-thalamic path is topographically organized, so that the mammilar medial nucleus projects ventrally to the AV, AM and laterally to the AD. The fibers of the lateral half of the path, which includes all fibers coming from the mammilar lateral nucleus and lateral half of the medial, project bilaterally. The rest are homolateral.

The main efferents are sent towards the cingulate circumvolution (limbic associative cortex). Axons are also sent to the prefrontal cortex, medial motor cortex, orbitary areas of the frontal cortex and areas of visual association.
2. The *Dorsomedial nucleus*. The afferents of the DM nucleus come from the olfactory bulb (DMmc), the amygdala (DMmc), the substantia nigra (DMpl), the pallidus (DMmc, DMpc), the superior colliculus –SC- (DMpl), the intralaminar thalamic nuclei and the dorsal row.

The connections of the prefrontal DM-cortex and frontal-DM cortex are excitatory - glutamatergic-, whereas the afferents coming from the pallidus and the substantia nigra are inhibitory - GABA-ergic- [9].

The DM nucleus makes reciprocal connections with diverse cortical areas where its fibers finish in layers I, III and VI. Of these cortices, the prefrontal and insular cortex (DMmc, DMpc), the cortex of association (DMmc) and the cortex of the ocular field (8 area) (DMpl) are important.
3. The *Lateral nuclear group*
Dorsal zone: the DL nucleus receives impulses from the hippocampus (through the fornix) perhaps from the mammilary bodies and associative areas of the parietal cortex. It projects to the cingulate gyrus and associative zones of the parietal lobe.

The afferents to the LP nucleus are not well known, but they seem to proceed from the adjacent nuclei of relay, in particular from VP, CGL of the SC nucleus and the secondary sensorial cortex (area 2) with reciprocal connections. The studies of retrograde transport indicate that the LP nucleus emits its efferents to associative areas 5 and 7 of parietal cortex [2]. It also projects to the visual cortex (areas 17, 18 and 19).

Ventral zone: The VA nucleus receives afferents fundamentally from the dentate nucleus of the cerebellum, the globus pallidus and the reticular portions of the substantia nigra and nonmotor areas like the SC. It also receives fibers coming from the intralaminar and mean line nuclei. The efferents go fundamentally to the intralaminar nuclei, 6, 8 and orbitofrontal areas.

The afferents to the VL nucleus fundamentally come from the deep cerebellar nuclei. The dento-thalamic system constitutes the main afferency. Although the pallidum-thalamic fiber system projects mostly onto the neurons of the VA nucleus, some fibers reach the VL nucleus. To this thalamic zone afferents also come from the prefrontal cortex, primary motor (area 4) and intralaminar nuclei. This nucleus sends its efferents towards the primary, premotor and supplementary motor cortices and nonprimary somato-sensitive areas in the parietal cortex (areas 5 and 7). Deep cerebellum nuclei project fundamentally to the VL and from the pallidus mainly to the VA.

The VP nucleus constitutes the main destination of mid lemnisco fibers, trigeminal lemnisco and the spino-thalamic path. The oral part of the VPLo nucleus receives projections from the contra-lateral deep cerebellum nuclei and projects to the primary motor cortex. The caudalis zone, VPLc, receives somato-sensorial afferents from the spinal cord and rachidian bulb nuclei through medial lemnisco and spino-thalamic paths. The VPM receives somatic afferents from face receptors and intraoral structures. The ascending trigeminal fibers arrive at this nucleus. Both nuclei, the VPL and VPM, also receive afferents from the primary somatosensorial cortex. Their efferents have one precise topical projection to the post-central circumvolution cortex, areas 3, 1 and 2 (sensitive homunculus).

4. The *Posterior nuclear group*. The pulvinar does not receive projections from the ascending long sensitive paths, except the inferior part of this nucleus at which a projection arrives from the superficial layers of the SC. The inferior part of this nucleus and the adjacent portion of the lateral pulvinar maintain reciprocal connections with the occipital cortex including the striated cortex. The projections of the inferior pulvinar to areas 17, 18 and 19 constitute the final connection in an extra-geniculated visual route. The lateral part of the pulvinar projects to the temporal cortex and receives reciprocal projections from the same region. The medial part projects to the superior temporary circumvolution.

The posterior pulvinar-lateral complex and DM nucleus are collectively known as the multimodal association thalamic nuclei. They can be considered

jointly both from the point of view of their connections and their functions. They receive projections from the retina and SC and are also related to associative cortex P-T-O and to visual areas of the cerebral cortex. From a functional point of view they are also related to the visual route and to the control of ocular movements.

The ventral part of the CGM receives the projections from the central nucleus of the inferior quadrigeminus (TCI) and its efferents go to the primary auditory cortex (area 41). This projection is tonotopically organized so that the low frequencies are located laterally and the high frequencies medially. Afferents to the dorsal region coming from the pericentral nucleus arrive fundamentally from the TCI. Its tonotopic organization is not as clear as that of the ventral region and it projects to the secondary auditory cortex (areas 22 and 42). The medial region receives the projections from the external nucleus of the TCI and it projects without tonotopy to all of the auditory cortex (areas 22, 41 and 42).

The CGL receives projections from the retina via the optical beam, projects to the calcarine cortex (area 17) through the geniculate-calcarin beam or visual radiation and receives cortico-geniculate fibers from the same area. To a lesser extent it projects to the associative adjacent visual areas. It establishes internuclear connections with the pulvinar. The retine-geniculate projections are topically organized. The superior quadrants of both retinas (inferior field of view) end in the superomedial half of the CGL. The inferior quadrants (superior field of view) end in the infero-lateral half of the nucleus.

5. *Mean-line nuclei*. The main afferents to these nuclei come from the hypothalamus, nuclei of the brain stem, amygdala and parahippocampal gyrus. They send their projections to the limbic cortex and the striatal ventral nucleus.

6. *Intralaminar nuclei*. They are classically considered as nuclei that receive and send projections in an unspecific or diffused way. Despite this, it is known that different portions receive various afferents and each one of them projects in a precise topographic way to the basal ganglia and specific zones of the cerebral cortex, thus being more specific than was believed [2]. The main afferents to these nuclei come from the reticular formation. The dento-rubrothalamic system (cerebellum) projects fundamentally to the VL and collaterals of this system project to the intralaminar nuclei. The VA nucleus receives its main input from the globus pallidum. Collaterals of this projection reach the intralaminar nuclei. Most of spinothalamic fibers and trigeminal lemnisci (ascending fibers of pain) project onto the VP, but also onto the intralaminar nuclei. These nuclei also receive cortical fiber projections coming from the motor and premotor areas. The fibers that originate in the motor cortex (area 4) finish in the neurons of the centremedian, paracentral and centrelateral nuclei. The ones that originate in the premotor cortex (area 6) conclude in the parafascicular and centrelateral nuclei. In contrast to other

thalamic nuclei, the connections between the intralaminar nuclei and the cerebral cortex are not reciprocal.

The main efferents of the intralaminar nuclei go to other thalamic nuclei (fundamentally reticular), to the striatum (caudate and putamen) and widely towards associative areas of the cerebral cortex. By special methods of retrograde marking it has been seen that a small number of intralaminar neurons project through collateral axons to distant cortical areas [10].

7. *Reticular nuclei*. They receive cortico-thalamic projections, but they lack thalamus-cortical projections. They are connected to many thalamic nuclei and in addition they are crossed, receiving collateral from thalamus-cortical and cortico-thalamic fibers and exerting therefore a modulatory action on thalamic neuronal activity.

Motor thalamus

The motor thalamus (MT) is defined as the thalamic region related to the subcortical motor areas (basal ganglia and the cerebellum) and cortical regions such as the primary motor cortex, supplementary motor area and the premotor cortex [11]. Considered surgically it includes the ventral thalamic region, which receives afferents from the cerebellum, the basal ganglia and the substantia nigra [12]. The term MT is used in stereotactic neurosurgery to make reference to the ventral thalamic region located along the anterior commisure-posteriorcommissure line between the external medullary lamina anteriorly and somatosensory nuclei posteriorly [13].

The MT refers to those nuclei that transmit information coming from the substantia nigra (subregion dorsalis), the globus pallidus (subregion oralis) and the cerebellum (subregion intermedia) to the prefrontal cortex, supplementary motor, premotor, motor and somatosensorial cerebral areas [14-16].

It is generally agreed, as shown in the previous definitions, that the location of the motor thalamus is in the ventral zone of the thalamus, where the nuclei receiving information coming from the basal ganglia and the cerebellum are also located and their main function consists of collaborating in processing motor information.

Classification of the motor thalamus nuclei

Different classifications of nuclei have been proposed for the MT, fundamentally based on cytoarchitectonic aspects and connection fibers in nonhuman primates and extended by analogy to the human thalamus from scientific data that indicate chemoarchitectonic similarities between them and therefore make the functional inferences possible [17, 18].

Hassler [19], based on cytoarchitectonic and myeloarchitectonic criteria, divides the MT into four parts: oral, caudal, intermediate and lateropolar, in turn subdivided into three regions: ventral, intermediate (central) and dorsal (table 3).

Table 3. Hassler`s classification of the motor thalamus.

Lateral thalamic nuclear region	NUCLEI		
	Ventral	**Intermediate (Central)**	**Dorsal**
Oral	**Ventro-oralis (Vo):** *anterior (Voa); posterior (Vop); internus (Voi); medialis (Vom)*	**Centrolateral oralis (Co)**	**Dorso-oralis (Do)**
Caudal	**Ventrocaudalis (Vc):** *anterior (Vca); posterior (Vcp); parvocellular (Vcpc); portae (Vcpor)*	**Centrolateralis caudalis (Cc)**	**Dorsocaudalis (Dc)**
Intermediate	**Ventrointermedius (Vim)**	**Centrolateralis Intermedius (Cim)**	**Dorso-int ermedius (Dim)**
Lateropolar	**Lateropolaris (Lpo):** *magnocellularis (Lpomc); basalis (Lpob)*		**Dorsalis superficialis (Dsf)**

This classification is widely used in the study of the human MT, and is shown in some of the stereotactic atlases of the human thalamus, like that of Schaltenbrand and Wahren [20].

Ilinsky and colleagues [21] offer a simpler alternative classification to that of Hassler, which extrapolates the anatomical and physiological experimental data of the human thalamus. For these authors, the pallidal projections to the human thalamus would include the Lpo and Voa; the nigral projections would correspond with the Lpomc nuclei and the anterior part of the Voi; and the projections from the cerebellum would include the Vop, Vim and the posterior part of the Voi of Hassler`s classification. Hiari and Jones [5, 16] define four main nuclei: 1 - *ventral anterior* (VA), consisting of two parts: *magnocellular* (VAmc) and *parvicellular* (VA); 2 - main ventral medial (VMp); 3 - *ventral lateral* (VL), subdivided into two regions: *anterior* (VLa) and *posterior* (VLp); and 4 - *ventral posterior lateral* (VPL) composed of an *anterior region* (VPLa) and a *posterior region* (VPLp). These nuclei receive afferents mainly originating in the substantia nigra (VAmc, VMp, and part of VA) the pallidus (VA and VLa), the deep cerebellar (VLp), deep lemniscal afferents (VPLa) and the superficial sensory lemniscal fibers (VPLp).

Ilinsky and Kultas-Ilinsky [12] divide the MT based on subcortical afferents into two large nuclei: 1 - *ventral anterior (VA)*, subdivided into three regions: magnocellular (VAmc), parvicellular (VApc) and densicellular (VAdc); and 2 - *ventral lateral (VL)*. The VAmc receives afferents from the substantia nigra pars reticulata; the VApc, from the globus pallidus internus and pars medialis; and the VL from the cerebellum.

Based on the afferents that the MT receives, it is divided into three territories: *cerebellum, pallidal and nigral* [15, 22]. Some authors indicate that it is a controversial division since the territorial organization of the human

thalamus has not been completely established and no agreement exists about the extension of the pallidal territory (generally rostral and caudal to the cerebellum territory), which varies from some studies to others [23]. For Macchi and Jones [16], the MT is divided according to cerebellum, pallidal and nigral afferents. The pallidal and nigral fibers go to the VA-VM and VLa nuclei, respectively, projecting posteriorly to the supplementary motor cortex, Brodmann`s 6 area and the prefrontal cortex, whereas the fibers coming from the cerebellum go towards the VLp making their way towards the primary motor cortex and part of the premotor cortex.

The use of classifications that incorporate numerous nuclear divisions within the MT favors neither understanding nor organization, increasing the confusion and making agreement between specialized professionals difficult. For this reason, other authors propose simpler classifications as is the case of Ilinsky an Kultas-Ilinsky [13], who after considering that in nonhuman primates this region is clearly delimited in function to subcortical afferents, have determined the following territories: nuclei that receive afferents from the basal ganglia (VApc and VAdc of the pallidus); nuclei that receive afferents from pars reticularis of the substantia nigra (VAmc); and nuclei that receive afferents from the cerebellum (VL).

Main connections of the motor thalamus

The MT receives projections fundamentally from the globus pallidus, the cerebellum and the substantia nigra. The modulation provided by these structures allows the planning, initiation and coordination of actions, as well as a guide and an appropriate conclusion of voluntary movements. In general, the zones of the thalamus that receive afferents from the pallidus and the substantia nigra project mainly towards the supplementary motor cortex and the afferents coming from the cerebellum project primarily to the motor cortex.

Palidal projections

From all the basal ganglia, the main afferents to the thalamus come from the globus pallidus. This nucleus consists of two segments: internal (GPi) and external (GPe). The GPi receives afferents from the caudate and the putamen and directly sends a projection to the thalamus (direct pathway). The GPe receives afferents originally from the caudate and the putamen, but it projects to the subthalamic nucleus; and this sends its projections to the GPi, which also projects its fibers to the thalamus (indirect pathway).

The activity of the corticostriatal projections produces, from the direct pathway, a GABA-ergic inhibition of the neurons of the GPi or the substantia nigra par reticulata that leads to a lack of inhibition of the thalamic nuclei or brain stem nuclei, facilitating the beginning of a certain movement [24]. The function of the indirect pathway would be the reduction of the motor activity

[25]. The activation of the striatum GABA-encephalinergic neurons causes an inhibition of the GPe that also inhibits the subthalamic nucleus. The deinhibition of this nucleus leads to the excitation of the GPi or the substantia nigra pars reticulata, increasing its input level and therefore its inhibitory capacity over the motor thalamus.

The fibers coming from the GPi that arrive at the motor thalamus contact mainly the VLa nucleus and another small group reaches the VA nucleus. The pallidal projections to the rostral nucleus of the ventral thalamic group are organized in a topographic way and they do not superpose either with the deep crossed cerebellum projection nuclei or with the ascending projections of the substantia nigra [2].

The rostromedial region of the GPi (limbic part of the nucleus) has contact with the rostral portion of the VApc and the rostral region of VLa and VM. The projections of the ventrolateral region of the GPi (sensitive-motor part of the nucleus) go to the VLa and a small fiber group arrives at the VA. The dorsal part of the GPi (associative part of the nucleus) sends its projections to the dorsal region of the VA and VLa [26]. The fibers that arrive at the thalamus coming from the pallidum go fundamentally to the supplementary motor cortex, which takes part in mechanisms that exert influence on muscular tone and modify posture, as well as acting on the automatic reflex response to pressure, bimanual coordination, the planning of motor activities and, perhaps, their initiation [2]. These pallid-thalamic fibers also project to the premotor cortex [22, 27], which relates to voluntary motor function dependent on sensorial afferents (visual, auditory, somatosensorial). The VLa sends projections to a lesser extent to the primary motor cortex [28].

Cerebellum projections

The cerebellum, along with the basal ganglia, the motor thalamus and the frontal cortex, takes part in a complex system whose fundamental mission is to guarantee the organization and execution of motor activity.

From the deep nuclei of the cerebellum (dentate, fastigial and interpositus) afferents are sent to the MT. These fibers must cross the mid-line so that the motor cortex of each hemisphere receives information from the contralateral cerebellum. Axons leave the superior cerebellum through the cerebellar peduncule, cross the mid-line at the mesencephalic level and then ascend to the thalamus. From there, cerebellar-thalamic fibers ascend following a lateral trajectory or through the H fields of Forel. Here the pallid-thalamic and nigro-thalamic fibers are joined forming part of the thalamic fascicle. Most of the fibers that access the thalamus do it from the inferior part and a small group from the anterior and posterior parts [15, 22, 29] up to the VLp nucleus (and to intralaminar nuclei) to continue their trajectory to the frontal cortex later. The posteroventral and posterodorsal regions of the VLp mainly send their

projections to area 4 of Brodmann and a small fiber group reaches premotor areas, the additional motor cortex [28] and even the prefrontal cortex [31]. The anteromedial region of the VLp fundamentally projects to premotor areas and the supplementary motor cortex, even reaching area 4 [28].

Studies made with monkeys indicate that VLp is the main nucleus that receives projections from the dentate and interpositus cerebellum nuclei contralaterally and from the fastigial nucleus bilaterally [30,32]. It seems that a topographic organization exists in such a way that the anterior part of the deep nuclei of the cerebellum projects to the posterolateral region of the VLp and the posterior part sends its projections to the anteromedial region of the VLp [30]. The VLp nucleus also receives spinothalamic [30, 33] and vestibular afferents [30, 32].

Nigral projections

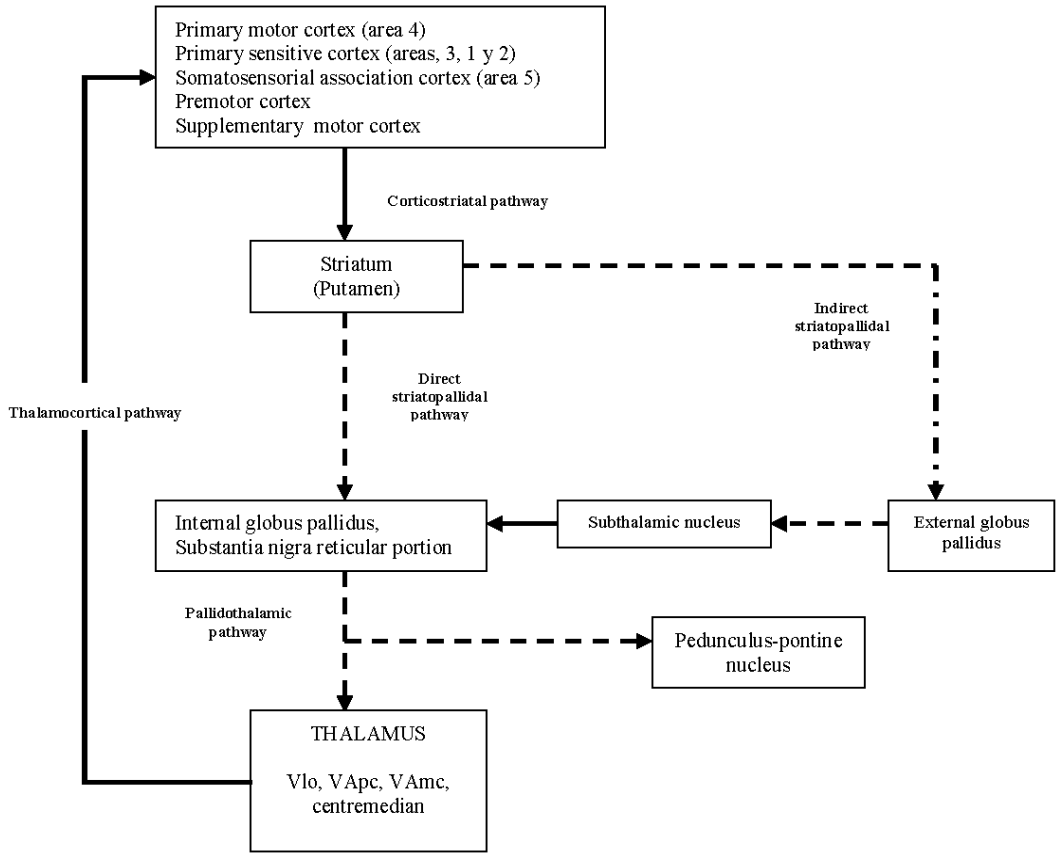
The substantia nigra is divided into two parts: compacta and reticulare. The nigrothalamic fibers originating in the reticular part project fundamentally to the VA nucleus and parts of the DM nucleus. The studies made in nonhuman primates indicate that these afferents to the MT, compared with the pallid and cerebellum projections, are smaller [22]. The nigral fibers that arrive at the thalamic ventral nucleus and go directly to the supplementary motor cortex, the frontal ocular fields and the additional frontal ocular fields [34,35].

Pathophysiology of the motor thalamus

The processing of motor information is carried out thanks to a circuit that connects the primary motor cortex, the supplementary motor area, the premotor cortex, the cingulate motor area and sensitive-motor areas with the basal ganglia, the cerebellum and the thalamus. The basal ganglia and the cerebellum, components of the motor system, influence the cerebral cortical activity through the thalamus.

The basal ganglia are involved in the selection, inhibition and sequencing of movements [24,36] and the cerebellum in the generation and execution of movements based on external sensorial keys [37].

The basal ganglia are organized in separate functional circuits (motor, oculomotor, prefrontal-dorsolateral, orbit-frontal and limbic), whose origin is located in different cortical areas. These project to separate regions of the basal ganglia and the thalamus and return to the same cortical areas of the frontal cortex where they originated. Of all the circuits, the so-called “motor circuit” (scheme 1) is essential in the programming, initiation and execution of movement and is implied in the development of motor disorders such as distonies, motor alterations in Parkinson’s disease and tremors. [38]. The GPi and the substantia nigra pars reticulata send inhibiting stimuli, using the GABA neurotransmitter, to motor control centers in the thalamus (ventrolateral and ventralanterior) and to the brain stem (peduncule-pontine nuclei). These



Scheme 1. Motor circuit. Continuous lines: excitatory. Discontinuous lines: inhibitory.

are in charge, through the neurotransmission with glutamate, of the stimulation of cortical modulator centers of movement (premotor area and supplementary motor area). The neostriatum (caudate and putamen) has receivers for the dopamine formed in the compact substantia nigra. In addition, the striatum modulates the action of GPi and substantia nigra pars reticulata through two pathways: a direct one, which, by the stimulation of D1 dopaminergic receivers, acts through the intermediary action of GABA restraining the GP, and another indirect pathway, which, as a result of the inhibition of D2 receivers, acts through GABA, restraining the external globus pallidus (GPe) which in turn acts by inhibiting the subthalamic nucleus. This, using glutamate, is the main stimulator center of GPi action and the substantia nigra pars reticulata [39].

Associated movement disorders as a result of alterations in the basal ganglia include a wide range of disturbances that go from the *hypokinetic or rigid-akinetic disorders*, characterized by poor movements as in Parkinson's Disease, to the *hyperkinetic or diskinetic disorders*, characterized by the existence of involuntary and inappropriate movements. Consequently, this range includes *tremor, chorea, ballisms, distonyc, mioclonies and tics*. It is postulated that in both cases an alteration of the *motor circuit takes place in the basal thalamus-cortical ganglia* [38].

The symptoms related to damage in the thalamus can be caused not only by injuries to the relay nuclei, but also by the interruption of the afferent systems. Thus, the cerebellum symptoms, involuntary movements, choreoathetotic and somatosensorial symptoms would also be associated with injuries located in the afferent MT and its afferent pathways. On rare occasions a pure cerebellum syndrome associated with injuries to the cerebellum VLp and their afferents or an extrapyramidal syndrome associated with injuries in the VLa and their pallidal afferents is observed. Injuries in the MT can cause alterations in the direction and coordination of movements (due perhaps to the disconnection with area 4 of Brodmann), muscular tone and planning of movements (disconnection of the premotor areas and supplementary motor cortex) [16].

Injuries in the thalamus can cause a great variety of movement disorders, including dystony, paroxysmal dystony, tremor, asterixis, ballism-chorea, pseudochoreoathetosis and myorhythmia [40-42].

One of the main sources of knowledge of the pathophysiology of the MT in humans comes from the results obtained in functional neurosurgery and in electro physiology recordings which in practice emphasize three goal zones for the treatment of movement disorders associated with Parkinson's disease, the treatment of the essential tremor, and several primary and secondary forms of distonies, these being the MT, the internal segment of the internal pallidum (GPi) and the subthalamic nucleus.

Studies indicate that in patients with cerebellum symptoms, the mid frequency of the neuronal activity of Vop and Vim is approximately between 10-15 Hertz [43]; in patients with Parkinson disease the neural activity of the MT does not vary significantly from one nucleus to another, being on average between 12 -14 Hertz [44-46] and in the cases of patients with distony, the firing rate of the cells of the MT is between 14 - 30 Hertz [47].

Parkinson's disease (PD)

According to the classic model of PD physiopathology, *akinesia and bradikinesia* are due to the output hyperactivity of the basal ganglia. The dopamine deficit in the nigrostriatum pathways seems to lead to a hyperactivity of the subthalamic nucleus and the GPi. For Lang and Lozano [39], the poor and intermittent arrival of dopamine to the neostriatum from the substantia nigra pars compacta in degeneration favors the inhibiting action of D2 receivers on the GPe which tends to a diminution of the normal inhibition of the subthalamic nucleus. Thus, it produces a large stimulation of the GPi and substantia nigra pars reticulata, which also forcefully restrains the action of the thalamus and brain stem and, therefore, the action of the cortical centers of motor control as well. With this in mind, the therapeutic use of pallidoctomy in PD is an attempt to interrupt the excessive inhibition of the thalamus by the

basal ganglia, secondary to the dopamine lost and therefore, facilitate the thalamic-frontal projection.

One of the theories on the physiopathology of tremor in PD pinpoints dopaminergic degeneration, or even other non-dopaminergic systems, which result in an oscillating system that includes the motor circuit of the basal ganglia, the cerebellum, the thalamus, and the somatosensorial and motor cortices [48].

Inhibitory projections leave from the GPi-substantia nigra pars reticulata to different thalamic nuclei that also constitute the origin of the last link of the motor circuit, sending glutamatergic projections to different areas of the cerebral cortex. The connection between the GPi-substantia nigra pars reticulata and cerebral cortex, via the thalamus, constitutes the most important mechanism through which the basal ganglia can influence cortical activity. The consequence of the hypofunction in the GPi-substantia nigra pars reticulata is the disinhibition of the thalamic neurons and the excessive activity of the reinforced influence of the basal ganglia on the motor cortex, which seems to be implied in the production of *discinesies*.

Studies made [49,50] with monkeys MPTP with discinesies induced by L-dopa or dopaminergic agonists indicate that the administration of these drugs would produce, through direct circuit, an overinhibition of the GPi and, through an indirect one, a diminution of the GABA-ergic inhibition on the Gpe that would be hyperactive. In turn, it inhibits the subthalamic nucleus causing a diminution in the excitation on the GPi. Thus, not only in the direct way but also in the indirect way, a diminution of the activity in the GPi and in the substantia nigra pars reticulata takes place and it ceases to inhibit the VA and VL nuclei of the thalamus, producing a hyperexcitation of the premotor cortex, resulting in the appearance of discinesies.

Good results with levodopa induced discinesies have been obtained when the Voa and Vop were used as surgical targets, whereas action on the Vim yields few therapeutic results [51].

The classic model of the basal ganglia predicts that pathological hyperactivity in the subthalamic nucleus happens as a result of the degeneration of the *nigrostriatal pathway*, resulting in a MT inhibition, which leads to an altered activity in the pallidum-thalamic inhibiting pathway [48, 52]. The thalamus-cortical inhibition gives rise to an inadequate operation of the somato-sensorial cortex with resulting *bradicinesia* [53]. Recent studies indicate that injuries to the MT reduce the tremor significantly but have a small effect on bradicinesia in PD [23].

The subthalamic nucleus and the GPi play a principal role in the generation of tremor, as is observed in studies made with monkeys, as well as in data collected from sterotactic surgery in humans [54]. The tremor in PD can also have a thalamic origin. Injuries or high frequency electrical

stimulation of the Vim or Vop (Ventralis oralis posterior) reduce tremor significantly [55]. The recordings of ventrolateral thalamus neuronal activity carried out in stereotactic surgery has shown the relation of this zone to the tremor and how most of the cells (78%) of the Vim and the Vop do not respond to sensorial stimuli [56]. These data are supported by the findings using noninvasive techniques that indicate a hypermetabolism in the anterior ventrolateral nucleus (Vop) [57]. In studies made with functional metabolic neuroimaging techniques, on PD patients with bilateral tremor, a specific metabolic network for the tremor has been found which includes the thalamus, the protuberance (pons) and the premotor cortex [58]. A VL nucleus thalamotomy reduces the amplitude of the tremor significantly in PD, confirming that the thalamus plays an important role in the generation and propagation of the tremor in this disease [23]. Injuries in the MT can improve the precision of the fine movements, probably as a result of the tremor healing. The execution of alternating fast movements does not get worse after thalamotomy, which suggests that the MT is not implied directly in the slowing of the repetitive movements observed in PD [23].

Essential tremor

The essential tremor is the most common form of involuntary movement. It can be a consequence of an exaggeration of normal physiological mechanisms, constitute the only symptom of the disease or be part of the symptomology of a great number of pathological processes of greater or smaller gravity. Usually it affects the hands but also other parts of the body (trunk, chin, legs, vocal cords, etc.).

From the cerebellum the fibers go to the Vop and Vim contralaterally, projecting fundamentally to area 4 of Brodmann. According to the data available, it is believed that this circuit is implied in the secondary tremor pathophysiology of different diseases. Injuries in the Vop/Vim alleviate the tremor in an unspecific way. The Vim is considered to be related to propioceptive sensitivity that receives afferents from the contralateral hemibody and displays a defined somatotopic organization: the region of the superior member is located medially and the inferior member dorsolaterally, in the region adjacent to the internal capsule [59].

The findings obtained after surgical injuries, cerebral deep stimulation and neuroimaging functional techniques suggest that the cerebellum and the thalamic nuclei that receive cerebellum projections are all related to the mechanisms of the essential tremor. The *cerebellum-thalamus-cortical* pathway is involved in the physiopathology of the essential tremor. Injuries or the deep stimulation of the Vim improve, and in many cases extinguish the essential tremor. Functional neuroimaging data show an increase in bilateral cerebellum and deep cerebellar nuclei activation [60, 61]. Since the cerebellar

inputs go fundamentally to the Vim and are excitatory by nature, the hyperactivity in the cerebellum of these patients could increase the activity in Vim [16]. The direct participation of the GABA-ergic system, as well as thalamic control of the cerebellar activity in the genesis of the tremor, is reflected in the PET studies made with 11C-flumazenilo, a marker of the GABA-ergic system activity, which show alterations in GABA receivers of the thalamus [62].

Molnar and colleagues [63] suggest that the physiopathology in the cerebellum-thalamus-cortical pathway could be a possible cause of the essential tremor. In this work they indicate that the firing rate of the Voa/Vop neurons, apparently receiving pallidal projections, is lower in PD patients than in patients with essential tremor, whereas the firing rate of the neurons of the Vim/Vpla in patients with essential tremor was increased, suggesting that this increase is pathological and would explain the effectiveness of injuries or deep stimulation in the Vim as effective treatment for essential tremor.

Dystonia

Dystonia is a movement disorder caused by an involuntary contraction and is maintained with torsion movements and abnormal positions in one or several regions of the body. From an etiological point of view dystonias may be classified as primary (hereditary or idiopathic) or secondary (neurologic diseases, inherited metabolic defects, traumatisms, tumors, toxins and drug intoxication, etc). Although the physiopathological base of dystonias is not well known and depends on multiple factors, it seems that the idiopathic origin of dystonias is in the basal ganglia and is a result of a hyperactivation of the direct pathway of the motor circuit that gives rise to exaggerated thalamus-cortical activity [64]. The putamen and the thalamus are affected in most patients with secondary dystonia. This movement disorder is one of the most frequent after focal thalamic injuries and predominantly affects the distal parts of the arms [65].

The findings of the effectiveness in the treatment of dystonias after injuries or deep stimulation of the VL nucleus (including the oral posterior ventral nucleus Vop and ventral interval, Vim), GPi and subthalamic nucleus suggest that these cerebral structures have an important role in their development. One of the possible hypotheses is a disturbance in the operation of the motor circuit *basal ganglia -thalamus-cortex.*

Neurophysiological studies with microelectrodes indicate that alterations in the neuronal activity of the basal ganglia and thalamus are associated with dystonias [66, 67]. It seems that anomalies in the frequency and the pattern of neuronal discharge (predominance of neurons that make high frequency discharges with posterior silence) are present in both segments of the globus pallidum and in the thalamus. Zhuang and collaborators [68] found that this

abnormal firing activity exists not only in the Vop/Vim and GPi, but also in the subthalamus of dystonic patients, and it is directly related to the development of dystonic movements.

Functional neuroimaging data confirm that an abnormal pattern of cerebral activity in cases of primary generalized dystonia exists, and is characterized by an increase in activity (increase in *regional cerebral blood flow*, rCBF) in the supplementary motor cortex and prefrontal cortex, especially in the dorsolateral zone [69-71]. This enhanced activity of these motor cortices may be a result of overactivity of the basal ganglia via increased output through the thalamo-cortical pathway.

This model is consistent with the hypothesis that an alteration in the preparation and selection of movements exists in dystonia [71]. This pattern of cerebral overactivation found in primary dystonias is different from the ones found in patients with PD in which a reduction of the cerebral activity in the additional motor cortex and prefrontal dorsolateral cortex is observed [72].

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