# Cerebellar Thalamic and Thalamocortical Projections

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### Abstract

Although it is well known that the major output of the cerebellum is directed to the thalamus and ultimately to the cerebral cortex, the anatomical details and functional organization of this system remains unclear. Here, the current status of the cytoarchitecture of the motor thalamus, its afferents and efferent cortical projections are reviewed. The distribution of the cerebellothalamic and pallidothalamic projections to motor cortical areas is also discussed and the functional importance of these motor systems is highlighted.

## Introduction

Thalamus as the gateway to the cerebral cortex occupies a pivotal place in the processing of incoming and outgoing signals. Over the past 20 years, interest in the organization of the motor thalamus increased due to its role in the amelioration of tremor and rigidity following either thalamotomy (Ohye and Narabayashi 1979; Tasker et al. 1982; Ohye 1997) or deep brain stimulation (Benabid et al. 1996; Hubble et al. 1997; Starr et al. 1998). Despite the importance of the motor thalamus in motor control functions, details of its anatomical organization including its afferent and efferent connections still remain to be addressed. Thalamic studies are often stymied by the difficulty in defining and clearly delineating its constituent nuclei and their borders. The lack of agreement on thalamic terminology and nomenclature has also contributed to the confusion (for review, see Percheron et al. 1996, Ilinsky and Kultas-Ilinsky 2002; Jones 2007). Thalamic nuclei can be defined based on cytoarchitecture and chemoarchitecture but the term motor

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thalamus refers to the projection territory of the basal ganglia (efferent projections of the substantia nigra and globus pallidus) and the deep cerebellar nuclei. Since these projections may not strictly adhere to nuclear boundaries, comparisons made from different experiments and based on different species are problematic. This is due, in part, to the difficulty in reliably delineating the boundaries of the motor thalamus across mammalian species since both the number and cytoarchitectural details of the constituent subnuclei vary across species (Jones 1985, 2007). Many studies compared results across different experiments and animals in concluding that the cerebellum and basal ganglia projections distributed to separate thalamic nuclei and that the thalamocortical projections to different motor cortical areas arose from separate thalamic nuclei (Schell and Strick 1984; Alexander et al. 1986; Jones 1985, 2007; Percheron et al. 1996). The primary problem with such comparisons is the uncertainty of applying the same thalamic nuclear boundaries across experiments. One way to address this uncertainty is to eliminate the need to delineate thalamic nuclear boundaries by directly evaluating overlap of the cerebellar and basal ganglia projections with thalamocortical projection neurons using multiple neuroanatomical tracers in the same animal. Here, a review of the afferent and efferent connections based on anatomical studies utilizing axonal transport techniques in primates with a particular emphasis on the comparison of the cerebellothalamic and pallidothalamic projections is presented. Results from experiments using transneuronal labeling are presented elsewhere in this volume and will not be reviewed here.

## Cyto- and Chemoarchitecture of the Motor Thalamus

According to the terminology of Olszewski (1952), the motor thalamus typically consists of the ventral anterior nucleus (VA), ventral lateral nucleus pars oralis (VLo), ventral posterior lateral nucleus pars oralis (VPLo), ventral lateral nucleus pars caudalis (VLc), ventral lateral nucleus pars medialis (VLm), and area X (X) in the macaque monkey. The cytoarchitectonic distinctions between these nuclei are somewhat vague and not readily agreed to by others who have proposed either more or less thalamic subnuclei (Walker 1938; Hassler 1982; Percheron et al. 1996; Ilinsky and Kultas-Ilinsky 2002; Jones 2007). An alternative approach to defining and naming thalamic nuclei was based on the distribution of afferent connections. Jones (2007) employed this criterion in proposing a terminology that might be applicable to both primate and non-primate species in his simpler nomenclature of the motor thalamus: VA and two subdivisions of VL: anterior and posterior where VLa primarily refers to the pallidothalamic territory and VLp, the cerebellothalamic territory. Some researchers have argued that a single VL should not contain both pallidal and cerebellar territories and that the nigral and pallidal thalamic projections to its primary targets should be subdivisions of a single basal ganglia–related entity such as VA (Percheron et al. 1996; Ilinsky and Kultas-Ilinsky 2002). The nomenclatures of Olszewski, Jones, and Ilinsky are compared in Table 24.1. Based on these differences, it is clear that thalamic parcellation and

**Table 24.1** Motor thalamic nomenclature

| Olszewski (1952) | VApc | VLo | VPLo | X(VLx) | VLc |
|---|---|---|---|---|---|
| Jones (2007) | VApc | VLa | VLp | VLp | VLp |
| Ilinsky and Kultas-Ilinsky (2002) | VApc | VAdc | VL | VL | VL |

nomenclatures remain far from standardized. In the following, the distinctive cyto- and chemoarchitectonic features of the motor thalamus using Olszewski's (1952) nomenclature and where directly applicable, the terminology of Jones (1985, 2007) is described.

The ventral lateral nucleus pars oralis (VLo) of Olszewski (1952) in the macaque monkey primarily occupies the region caudal to the VA, rostral to the ventral posterior lateral thalamus (VPL), and lateral to the internal medullary lamina. Its cytoarchitecture is diverse consisting of multiple subnuclei depending on the author (Walker 1938; Hassler 1982; Percheron et al. 1996). The VLo corresponds to the ventral lateral nucleus anterior division (VLa) of Jones (1985) and consists of small-to-medium-sized, darkly stained cells packed irregularly as seen in Nissl preparations. Cells of VLo can be distinguished from the more posterior ventral posterior lateralis nucleus pars oralis (VPLo) because the latter contains larger cells with a sparser and more homogeneous distribution. Cells of VLo are also distinct from the ventral lateral nucleus pars caudalis (VLc) in that the VLc cells are darkly stained for Nissl and smaller. A medial division of VPL (area X) was also identified by Olszewski (1952) and is characterized by the presence of small, homogeneously distributed, lightly Nissl stained cells. These subnuclei, VPLo, VLx, VLc, described by Olszewski together form the single VLp nucleus of Jones. Since the differences between these subnuclei are variants on a common theme and together these nuclei form a cerebellar projection to the motor cortex, Jones (1985) suggested the single designation VLp.

The subnuclei of the motor thalamus are difficult to distinguish based on Nissl cytoarchitecture alone but differential staining within the motor thalamus has been found using a variety of histochemical and immunocytochemical stains. Acetyl-cholinesterase (AChE) staining greatly facilitates the comparison between VLo and VPLo (Fig. 24.1). The VLo (VLa) stains dark for AChE contrasting sharply with the lighter AChE staining in VA rostrally and moderately stained VPLo (VLp) caudally. The differential AChE staining is most apparent in the owl monkey thalamus (Stepniewska et al. 1994; Sakai et al. 2000) in comparison to the macaque monkey thalamus (Sakai et al. 2003; Jones 2007). Differential immunocytochemical reactivity to the monoclonal antibody, CAT 301, is also found where high immunoreactivity is found in VPLo (VLp) and low in VLo (VLa) in the macaque monkey thalamus (Fig. 24.1) (Hendry et al. 1988; Stepniewska et al. 2003). Subnuclei of the motor thalamus are also immunoreactive for calcium-binding proteins. Low calbindin immunoreactivity is found in VPLo and VLx whereas VLo and VLc were moderately to strongly immunoreactive (Percheron et al. 1996; Stepniewska et al. 2003; Calzavara et al. 2005; Jones 2007). Jones reported high parvalbumin immunoreactivity in VLp and moderate to weak immunoreactivity in VLa whereas
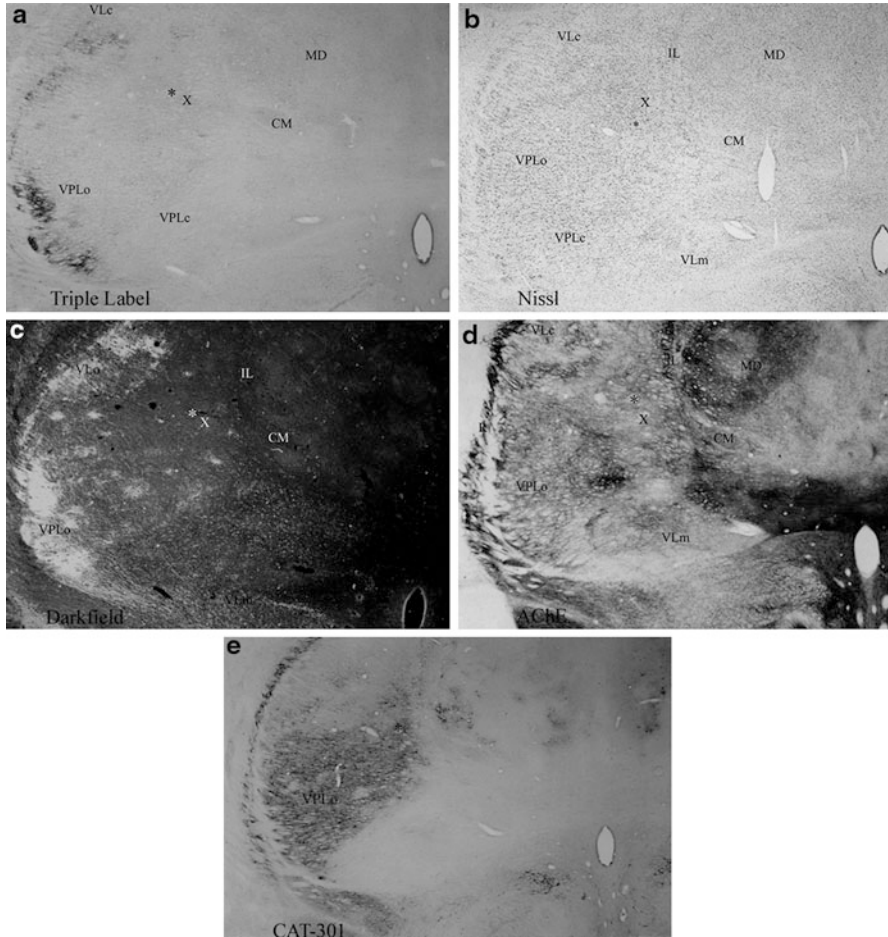
**Fig. 24.1** Low power photomicrographs of a series of coronal sections through the macaque motor thalamus. (**a**) Brightfield photomicrograph of a section showing cerebellothalamic wheat germ agglutinin conjugated horseradish peroxidase (WGA-HRP) labeling in VPLo and the patches of pallidal biotinylated dextran amine (BDA) labeling in VLc. Asterisks denote the same blood vessel in A-E. (**b**) Major cytoarchitectonic features of the motor thalamus at this thalamic level in a cresyl violet stained section. (**c**) Darkfield photomicrograph of the same section shown in A. Patchy cerebellar and pallidal labeling in VLc interdigitate. (**d**) Acetylthiocholinesterase (AChE) chemoarchitecture stained section. (**e**) The adjacent section immunoreacted for CAT 301. Note that VPLo is immunopositive for CAT 301 (Modified from Sakai et al. (2003). Ascending inputs to the pre-supplementary motor area in the macaque monkey: cerebello- and pallido-thalamocortical projections. Thalamus Related Syst 2: 175–187 with permission)

Calzavara et al. (2005) found that parvalbumin immunoreactivity in VLo with dense and patchy immunoreactivity was found in VLx, VPLo, and VLc. The patchy immunoreactivity of dense and light staining, particularly in medial VLx, VLc and along the VLo and VPLo border lead Calzavara et al. (2005) to suggest that

parvalbumin immunoreactivity is of limited value in delineating the motor thalamic subnuclei. In summary, cytoarchitectonic criteria combined with either AChE, CAT 301 or calbindin immunoreactivity enhance delineation of the motor thalamus, particularly the distinction between VLo and VPLo.

## Afferents of the Motor Thalamus

The motor thalamus can be defined based on its afferent projections from the cerebellum and globus pallidus. Many studies have examined the cerebellothalamic distribution in the macaque monkeys using silver degeneration methods following cerebellar lesions and anterograde axonal transport techniques (Kusama et al. 1971; Mehler 1971; Chan-Palay 1977; Stanton 1980; Kalil 1981; Asanuma et al. 1983a, b; Ilinsky and Kultas-Ilinsky 1987). There is general agreement that the cerebellothalamic projections distribute in a lamella-like arrangement composed of rod-like zones of axonal terminations from the dentate nucleus and more diffuse and focal terminations from interpositus and fastigial nuclei (Kalil 1981; Asanuma et al. 1983b; Mason et al. 2000). These terminal projections arise from the contralateral dentate and interpositus nuclei and the fastigial nuclei bilaterally (Stanton 1980; Kalil 1981; Asanuma et al. 1983a, b; Rouiller et al. 1994; Sakai et al. 1996). Both the dentate and interpositus nuclei densely project to contralateral thalamus while the projections from fastigial nucleus are sparser in comparison (Kalil 1981; Asanuma et al. 1983a, b).

The cerebellar nuclei project to the motor thalamus in a topographic manner whereby anterior regions of the cerebellar nuclei primarily project to lateral motor thalamus and posterior parts of the cerebellar nuclei preferentially project to medial motor thalamus (Stanton 1980; Kalil 1981; Asanuma et al. 1983a). The dentate and interpositus nuclei give rise to fibers that project to overlapping thalamic domains but it is not currently known if these inputs converge onto the same thalamic neurons in the monkey. Although a dorsoventral topography from the dentate nucleus has been described (Middleton and Strick 1997), an analysis of the fibers from the ventral dentate has shown that they distribute throughout the VL region (VLp of Jones) (Mason et al. 2000).

It has been suggested that each cerebellar nucleus contains a somatotopic body representation (Asanuma et al. 1983a; Middleton and Strick 1997; Jones 2007). Recent evidence suggests that a point to point somatotopy arising from each cerebellar nucleus to the motor thalamus may not completely characterize these projections. Based on small injections of retrograde tracers into the motor thalamus of the macaque monkey following electrophysiological identification of the face, forelimb, or hind limb representation, Evrard and Craig (2008) suggest that the cerebellar projections can be more aptly described as somatotopographic reflecting their finding that these projections both diverge and converge within the thalamus in a pattern that includes limited foci as well as broadly dispersed patches. This pattern of focal and widely distributed axonal fields was also reported using biotinylated dextran amine (BDA) labeling of the cerebellothalamic axons (Mason et al. 2000).

These data suggest that the afferent information arising from the cerebellar nuclei include both detailed somatotopically organized information as well as more generalized topographical information. Taken together, this anatomical distribution may best reflect the information processing required in order to produce coordinated multi-joint movements (Evrard and Craig 2008).

The majority of cerebellothalamic fibers cross midline at the brachium conjunctivum and travel anteriorly to the diencephalon. Dense bundles of cerebellar fibers turn dorsally coursing through the fields of Fórel in approaching caudal thalamus. At this level, a contingent of fibers continues dorsally through the zona incerta, traversing the ventral posterior inferior nucleus (VPI) and traveling on to caudal intralaminar nuclei and the mediodorsal (MD) nucleus. The main bundle of cerebellar fibers courses rostrally to the external medullary laminae to successively disperse at multiple caudorostral levels to the motor thalamus including VPLo, VLx, and VLc (Stanton 1980; Kalil 1981; Asanuma et al. 1983a; Mason et al. 2000). As noted earlier, analysis of cerebellothalamic terminals reveal two primary types of fibers: fibers with focal terminal fields and those with dispersed terminal fields (Mason et al. 2000). A single cerebellothalamic axon may emit several long branches with individual terminal fields consisting of clusters of elongated discs (Kalil 1981; Mason et al. 2000). An axon could give rise to as many as 29 terminal fields and close to 300 terminal boutons are associated with a single cerebellothalamic axon (Mason et al. 1996, 2000). Cerebellothalamic terminals are large, filled with round vesicles, and make asymmetrical contacts onto dendrites of thalamocortical projection neurons or interneurons (Harding and Powell 1977; Kultas-Ilinsky and Ilinsky 1991; Mason et al. 1996; Ilinsky and Kultas-Ilinsky 2002). The putative neurotransmitter is glutamate. Although no direct evidence is available in primates, a recent study reported VGlut2 immunoreactivity associated with the cerebellothalamic projections in the rat (Kuramoto et al. 2011).

There is some disagreement as to the extent of cerebellar projections to VLo with some investigators reporting this projection (Kusama et al. 1971; Mehler 1971; Chan-Palay 1977; Stanton 1980; Kalil 1981) and others denying it (Percheron 1996; Asanuma et al. 1983a; Ilinsky and Kultas-Ilinsky 1987; Jones 2007). If cerebellothalamic projections distribute to rostral motor thalamus including VLo as suggested by single tracing studies, then the possibility remains that thalamus receives overlapping and possibly converging inputs from the globus pallidus and cerebellum. A direct assessment of this question was made by using two anterograde tracers, one injected into the globus pallidus and the other injected into the deep cerebellar nuclei. The distribution of the axonal labeling emanating from each source is then directly compared (Rouiller et al. 1994; Sakai et al. 1996) (Fig. 24.2). In general, the pallidothalamic projections distribute broadly throughout VLo with small patchy foci found rostrally in the ventral anterior nucleus pars principalis (VApc) and VLc. Cerebellothalamic territory extends anteriorly beyond the cell-sparse zones of VPLo, VLx, and VLc. The double labeling method revealed some interdigitation of pallidothalamic and cerebellothalamic labeling in VLo, VLc, VLx, and VPLo (Rouiller et al. 1994; Sakai et al. 1996). These small interdigitating patches of pallidal and cerebellar projections are limited and occur preferentially
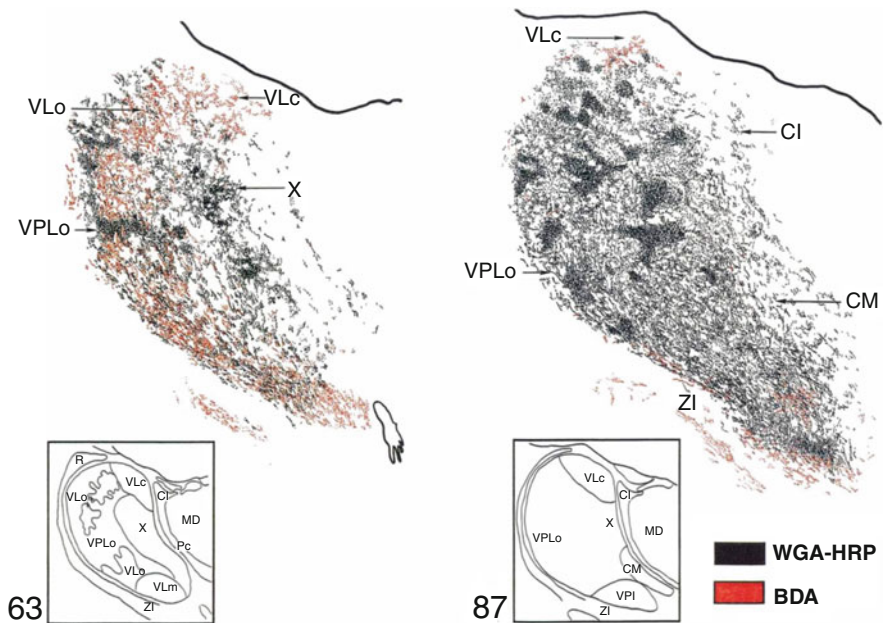
**Fig. 24.2** Line drawings of coronal sections showing the distribution of cerebellothalamic (*black*) and pallidothalamic projections(*red*) in motor thalamus. Cerebellar labeling is a result of WGA-HRP injections into the contralateral cerebellar nuclei and BDA injections were made into the internal segment of the globus pallidus (GPi). Major cytoarchitectonic delineations are shown for each thalamic level in the corner insets. In section 63, the cerebellar labeling is dense and patchy in VPLo and VLx and pallidal labeling is present in VLo and VLc. More posteriorly in thalamus as seen in section 87, the cerebellothalamic projections are prominent in VPLo, VLx and VLc while pallidal projections decline in VLc (From Sakai et al. (1996) Comparison of cerebellothalamic and pallidothalamic projections in the monkey (*Macaca fuscata*): a double anterograde labeling study. J Comp Neurol 368: 215–228 with permission)

along border zones between nuclei. Although zones of interdigitating inputs were observed in close apposition to the proximal dendrites and soma of the same neuron, this was very rare. Based on electrophysiological evidence, it is unlikely that single thalamic neurons receive converging inputs from the cerebellum and globus pallidus (Yamamoto et al. 1984; Nambu et al. 1988, 1991; Anderson and Turner 1991; Jinnai et al. 1993).

While it seems clear that the projections arising from the globus pallidus and those arising from the cerebellar nuclei primarily distribute to separate thalamic territories, individual thalamic nuclei receive differentially weighted inputs from these sources (Rouiller et al. 1994; Sakai et al. 1996). One explanation of these findings is that finger-like cell groupings characteristic of VPLo extend rostrally and irregularly into VLo (Asanuma et al. 1983a; Calzavara et al. 2005; Jones 2007) and may account for some of the discrepancies in the reports of the cerebellothalamic distribution. At the same time, the small foci of cerebellar labeling observed in the most rostral motor thalamus seem unlikely to be rostral

extensions of VPLo (Rouiller et al. 1994; Sakai et al. 1996). Nonetheless, areas of overlapping pallidal and cerebellar projections were rare (Sakai et al. 1996). Finally, it should be noted that VLc is a nucleus that receives a patchy and complementary pattern of labeling (Rouiller et al. 1994; Sakai et al. 1996). In this regard, it is of interest that a direct correspondence between the cerebellothalamic territory and negative calbindin immunoreactivity is found in VPLo and much of VLx (Calzavara et al. 2005). These authors found a complementary pattern of patchy cerebellar projections and areas of calbindin-poor immunoreactivity in VLc. These results suggest that calbindin immunohistochemistry may be helpful in delineating the cerebellar territory without regard to the constraints imposed by cytoarchitectonic analysis (Calzavara et al. 2005).

Although the bulk of the cerebellothalamic projections target the motor thalamus, cerebellar axons also distribute to MD and the intralaminar nuclei. Dense bundles of cerebellar fibers ascend through the fields of Forel, pass through the centrum medianum (CM), and distribute to the central lateral (CL) and to the paralamellar portion of MD (Asanuma et al. 1983a, b; Rouiller et al. 1994; Percheron et al. 1996; Sakai et al. 1996; Mason et al. 2000). The distribution of cerebellothalamic fibers arising specifically from the ventral dentate nucleus to MD is quite limited, and very little labeling is noted in MD other than its most lateral paralamellar portion (Mason et al. 2000).

## Motor Thalamic Projections to Cortex

The primary target of the motor thalamus is cortex lying anterior to the central sulcus. The general topography of the thalamocortical projections has been known for some years (Kievit and Kuypers 1977), but the extent of divergence and convergence of the thalamocortical projections as well as whether cerebellum or globus pallidus is a source of afferents to those projections is not completely known. The following will review the source of thalamocortical projections to the motor and premotor areas in nonhuman primates.

### Projections to MI

It has long been known that the primary cortical projection of the cerebellothalamic projections is to the primary motor cortex (MI) (for review, see Jones 2007) (Fig. 24.3). Typically, studies use microstimulation to map the body representation within MI (cytoarchitectonic area 4) in order to identify the sites for retrograde axonal tracer injections. These studies report that thalamic projections from VPLo, VLx, and VLc project to the primary motor cortex (Schell and Strick 1984; Wiesendanger and Wiesendanger 1985; Matelli et al. 1989; Darian-Smith et al. 1990; Tokuno and Tanji 1993; Rouiller et al. 1994; Morel et al. 2005). Moreover, when these experiments are combined with anterograde tracer injections into the cerebellar nuclei, the cerebellothalamic pathway is directly demonstrated revealing that the cerebellothalamic projections coincide with MI thalamocortical projections primarily in VPLo, but with decreasing coincidence of labeling in VLx, VLc, and
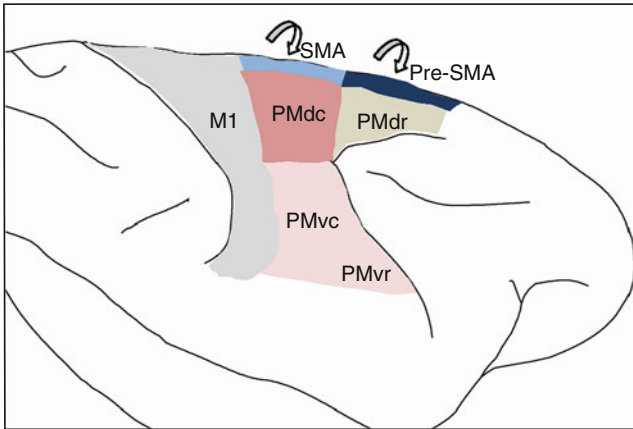
**Fig. 24.3** Schematic drawing of the motor cortical areas shown on a dorsal view of the macaque monkey brain. The motor cortical areas include: the primary motor cortex (MI), rostral and caudal subregions of the dorsal (PMd) and ventral premotor areas (PMv), and the pre-supplementary motor (pre-SMA) and supplementary motor areas (SMA) located on the mesial surface of the hemisphere

VLo (Rouiller et al. 1994; Sakai et al. 2002; Stepniewska et al. 2003) (Fig. 24.4). In addition, a generalized somatotopic organization is observed with the face represented medially and the leg laterally.

The idea that cortical areas receive mixed inputs derived from multiple thalamic nuclei was first proposed by Kievit and Kuypers (1977) and later by Darian-Smith et al. (1990). However, it was also proposed that ascending information from the cerebellum and globus pallidus project via parallel and separate pathways to the thalamic nuclei which in turn project to separate motor cortical fields including MI and the supplementary motor area (SMA) (Jones 1985; Ilinsky and Kultas-Ilinsky 1987; Alexander and Crutcher 1990). These results and other similar studies used retrograde tracers to label the thalamocortical neurons and then compared the distribution of labeling with reports of pallido- and cerebellothalamic projections (Schell and Strick 1984; Darian-Smith et al. 1990; Shindo et al. 1995). However, overlapping projections arising from the cerebellar territory and pallidal territory to a single cortical field had been proposed based on single labeling (Nambu et al. 1988, 1991; Matelli et al. 1989; Darian-Smith et al. 1990; Holsapple et al. 1991; Inase and Tanji 1995; Shindo et al. 1995) and multiple labeling experiments (Rouiller et al. 1994; Sakai et al. 1999, 2002). These latter studies showed that MI thalamocortical and cerebellothalamic projections overlap extensively, but regions of overlapping MI thalamocortical cells with pallidothalamic projections are also noted. The regions of overlapping cerebellar and pallidal thalamocortical projections tend to occur within the border areas particularly between VPLo and VLo (Fig. 24.4). As noted earlier, this labeling may be due to the difficulty in distinguishing the cell sparse interdigitating fingers of VPLo (Jones 2007), but the extent to which pallidothalamic projections reach MI remains controversial.
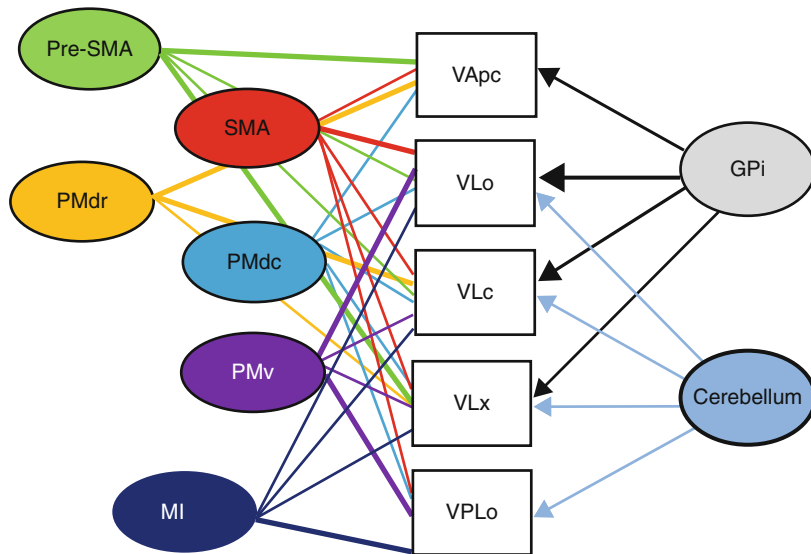
**Fig. 24.4** Schematic summary diagram showing the distribution of cerebellothalamic and pallidothalamic projections to motor thalamus and the thalamocortical projections to the motor cortical areas in the macaque monkey. The major input from the dentate and interpositus nuclei is to the contralateral VPLo, VLx, VLc while the major input from the internal segment of the globus pallidus (GPi) is the VLo and VApc. The motor thalamus provides primary input to the motor cortical areas: MI receives dense projections from VPLo, and also VLx and VLc, SMA receives dense input from VLo, pre-SMA receives primary input from both VApc and VLx, PMdr receives primary input from VApc and VLc while PMdc receives primary input from VApc and VLo, and PMv receives primary input from VLo and VPL. Motor cortical areas largely receive mixed and weighted input derived from GPi and cerebellum. The gradient in the projection densities is roughly indicated by the thickness of the *arrows* (Data from Morel et al. 2005 Divergence and convergence of thalamocortical projections to premotor and supplementary motor cortex: a multiple tracing study in the macaque monkey. Eur J Neurosci 21: 1007–1029; Sakai et al. 2002 The relationship between MI and SMA afferents and cerebellar and pallidal efferents in the macaque monkey. Somatosens Mot Res 19: 139–148; Sakai et al. 2003 Ascending inputs to the pre-supplementary motor area in the macaque monkey: cerebello- and pallido-thalamocortical projections. Thalamus Related Syst 2: 175–187 with permission)

Earlier studies noted that rostral MI, including the proximal forelimb representation, primarily receives thalamic projections from VLo whereas caudal MI, lying within the rostral bank of the central sulcus and containing the distal forelimb representation, primarily receives thalamic projections from VPLo (Matelli et al. 1989; Darian-Smith et al. 1990; Tokuno and Tanji 1993). In contrast, Holsapple et al. (1991) proposed that the caudal MI within the rostral bank of the central sulcus receives input predominantly derived from the globus pallidus via VLo. A preponderance of pallidothalamocortical projections to MI sulcal cortex has not been reported elsewhere, perhaps because few studies have systematically injected the sulcal cortex. However, coincidence of pallidothalamic projections

with the digit representation of MI sulcal cortex was noted in VLo using multiple labeling techniques (Stepniewska et al. 2003).

## Projections to SMA and pre-SMA

Cerebellothalamic projections extend beyond MI to project to other motor cortical fields including premotor cortex and supplementary motor areas. The supplementary motor area was originally thought to reside within the mesial cortex anterior to MI and posterior to the frontal granular cortex (Penfield and Welch 1949; Woolsey et al. 1952). However, the traditional SMA has been further subdivided into the rostral pre-supplementary motor area (pre-SMA) and caudal SMA based on distinctive functional and anatomical features (Matsuzaka et al. 1992; Tanji 1994; Matsuzaka and Tanji 1996; Picard and Strick 1996; Sakai et al. 2003) (Fig. 24.3). The SMA is microexcitable cortex but at higher current thresholds than those effective in MI. In contrast, pre-SMA is less responsive to even higher microstimulation currents.

Although previous work suggested that the SMA was primarily influenced by the basal ganglia outflow (Schell and Strick 1984), other studies reported thalamic afferents arising from multiple nuclei, including those nuclei that receive cerebellar input (Yamamoto et al. 1984; Wiesendanger and Wiesendanger 1985; Nambu et al. 1988, 1991; Darian-Smith et al. 1990; Matelli et al. 1989, 1996; Tokuno et al. 1992). The afferent distribution of the SMA thalamocortical cells was determined using a triple labeling paradigm whereby the pallidal and cerebellar afferents were labeled using two different anterograde tracers, and the SMA thalamocortical cells were labeled using a retrograde tracer following physiological identification of the hand/arm representation in SMA (Sakai et al. 1999). The interrelationship between the afferent sources and the retrogradely labeled neurons could be directly assessed using this paradigm. The SMA receives primarily afferents arising from VLo coincident with pallidal projections but it also receives some afferents from VLc, VLx, and VPLo, coincident with cerebellar projections (Fig. 24.4). Similar results were reported by Rouiller et al. (1994) based on multiple labeling methods.

Because the thalamic projections to MI and SMA arise from overlapping regions, the possibility that these projections might originate from the same neuron required further study. The direct comparison of the ascending projections from the pallidal and cerebellar sources to MI and the supplementary motor area (SMA) using multiple labeling methods revealed that MI and SMA receive predominant thalamic input originating from the cerebellum and globus pallidus, respectively (Rouiller et al. 1994; Sakai et al. 2002) (Fig. 24.4). MI and SMA also received secondary afferent input but evidence of collateralized projections from thalamus to MI and SMA was rare (Darian-Smith et al. 1990; Rouiller et al. 1994; Shindo et al. 1995; Sakai et al. 2002; Morel et al. 2005).

The projections to the pre-SMA have also been evaluated using multiple labeling techniques. The pre-SMA occupies the mesial cortex rostral to the SMA and is functionally distinct from SMA in that its neurons are responsive during movement preparation (Tanji 1994; Matsuzaka and Tanji 1996; Picard and Strick 1996) and in updating the temporal order of movement events (Shima and Tanji 1998, 2000).

Using multiple labeling techniques, the pre-SMA receives ascending inputs from both the cerebellum and globus pallidus by way of the motor thalamus in both the owl monkey (Sakai et al. 2000) and macaque monkey (Sakai et al. 2003) (Fig. 24.4). These results were similar to those reported by Matelli and Luppino (1996) who used fluorescent tracers to retrogradely label these thalamocortical neurons. The pre-SMA inputs primarily arose from caudal VA in the pallidothalamic territory and VLx in cerebellothalamic territory.

## Projections to the Premotor Cortex

The premotor cortex consists of the cortex lying rostral to MI and is coincident with cytoarchitectonic area 6. The spur of the arcuate sulcus roughly divides the premotor cortex into dorsal and ventral subdivisions (Fig. 24.3). The dorsal premotor cortex (PMd) lies medial to the spur of the arcuate sulcus and extends as far medially as SMA while the ventral premotor cortex (PMv) lies lateral to the spur. In addition, the PMd and PMv can be further subdivided into rostral and caudal divisions. These subdivisions differ anatomically based on cytoarchitectonic and histochemical differences (Barbas and Pandya 1987; Matelli et al. 1985, 1989; Matelli and Luppino 1996; Kurata 1994; Stepniewska et al. 2007) and functionally (Kurata and Tanji 1986; Rizzolatti et al. 1988; Preuss et al. 1996). Recently, the distribution of thalamic afferents to the premotor subdivisions has been re-evaluated using multiple labeling techniques in conjunction with quantitative methods. These analyses reveal that each premotor subdivision receives a predominant thalamic input and secondary, less dense afferents derived from multiple thalamic nuclei. The PMd receives afferents from motor thalamus including VLo, VLx, and VLc (Morel et al. 2005; Stepniewska et al. 2007) as well as VApc (Kurata 1994; Matelli and Luppino 1996; Rouiller et al. 1999; Morel et al. 2005; Stepniewska et al. 2007). A topographic shift in the distribution of thalamocortical projections is noted in comparison of the rostral and caudal PMd afferents (Fig. 24.4). Rostral PMd preferentially receives projections from VApc, VLc, and MD whereas caudal PMd preferentially receives projections arising from VLo (VLa in Morel et al. 2005) in the macaque monkey and VLa and VLx in the owl monkey (Stepniewska et al. 2007). Rostral and caudal sectors of PMv also receive differentially distributed afferents: rostral PMv receives predominant input from MD with less dense input from VApc, and VLo and caudal PMv receive predominant afferents from VLo and VLc (Morel et al. 2005). Others have noted significant input arising from VLx to PMv (Matelli et al. 1989; Rouiller et al. 1999; Stepniewska et al. 2007).

   Taken together, these data demonstrate that sectors of PM receive differentially weighted thalamic inputs. Morel and others (2005) speculated on the extent of divergence and convergence in the cortex by analyzing the degree of overlap and segregation in the thalamocortical projections. They suggest that the degree of thalamic overlap varies in the PM subdivisions with gradients of increasing projections from MD to rostral PM and from VLo and VPLo to caudal PM. To some extent, the degree of overlap in thalamus is related to the proximity of the cortical area. For example, greater overlap in thalamus was noted from adjacent cortical

areas such as between rostral and caudal PMv (Morel et al. 2005), caudal PMd and SMA (Rouiller et al. 1999), and pre-SMA and rostral PMd (Rouiller et al. 1999).

The thalamic inputs to the PM subdivisions cross cytoarchitectonic boundaries and arise from nuclei receiving afferent inputs from the cerebellum and the globus pallidus. The information from these sources is likely to overlap in the cortex. Since the predominant input to both VLx and VPLo originates from the cerebellum and these nuclei, in turn, provide afferents to PM subdivisions, these cortical subdivisions receive cerebellar inputs, albeit of differing strengths (Morel et al. 2005; Stepniewska et al. 2007). Similarly, since the nuclei, VApc, VLo, and VLc, all receive pallidal input and in turn, project to PM, these cortical regions also receive inputs derived from the globus pallidus. In this manner, the PM subdivisions receive mixed inputs from these sources.

## Projections to Other Cortical Areas

The cerebellar thalamic territory also projects to other cortical areas. The VLx gives rise to a small percentage of cells projecting to the frontal eye field (area 8) and even fewer to area 45 (Contini et al. 2010). The VLc projects to the posterior parietal cortex, in particular, the superior parietal lobule (Miyata and Sasaki 1983; Schmahmann and Pandya 1990). A small number of labeled cells in VLx and VLc were noted projecting to prefrontal cortical areas 9 and 46 using conventional neuroanatomical tracers (Middleton and Strick 2001). As described earlier, cerebellar afferents also distribute to the central lateral nucleus (CL) and the lateral part of MD (Fig. 24.2). Cells of the central lateral nucleus of the intralaminar group project to all of the motor areas and cells in lateral or paralamellar MD project to more rostral cortical areas including motor, frontal eye fields, and prefrontal cortex (Matelli et al. 1989; Darian-Smith et al. 1990; Schmahmann and Pandya 1990; Shindo et al. 1995; Matelli and Luppino 1996; Morel et al. 2005; Stepniewska et al. 2007; Contini et al. 2010).

## General Topography of Projections

Each motor cortical area receives differentially weighted inputs arising from the thalamic territories receiving cerebellar and pallidal afferents (Fig. 24.4). These inputs represent a unique mixture of afferents arising from multiple thalamic nuclei. However, there is considerable overlap in the afferent distribution to adjacent cortical areas, especially from border zones between cortical areas. A general topography corresponding to functional gradients within the motor areas has been previously noted (Matelli et al. 1989; Matelli and Luppino 1996; Rouiller et al. 1999; Morel et al. 2005). Traditional views of the motor cortical areas propose that these areas are hierarchically organized with MI involved in movement execution and the remaining motor cortical areas engaged in higher order aspects of motor control. The PMd and PMv have been associated with different roles in the selection and planning of movement (Wise et al. 1997; Hoshi and Tanji 2007), while the SMA is involved with internally generated movement sequences (Mushiake et al. 1991; Tanji 1994; Shima and Tanji 1998). The pre-SMA is hypothesized to participate in movement preparation and in updating the temporal

order of movement events (Matsuzaka et al. 1992; Matsuzaka and Tanji 1996; Shima and Tanji 1998, 2000). Despite the distinctly hierarchical functions attributed to each of these areas, recent accounts suggest a modification of this view. Functional analyses of the results obtained from varying microstimulation parameters suggest that the motor cortex processes information required for activating multiple muscles and movements (Schieber 2001; Graziano 2006; Graziano and Afalo 2007). Rather than a focal somatotopic organization of hierarchically organized areas, the motor cortex contains multiple, overlapping, and fractured representations that are suggested to provide the substrate for the production of coordinated synergistic movements within a broad topography (Sanes and Donoghue 2000; Schieber 2001, 2002; Graziano 2006; Graziano and Afalo 2007). Anatomically, a distributed network of diverging and converging connections may well provide the necessary substrate (Schieber 2001; Graziano 2006; Graziano and Afalo 2007; Evrard and Craig 2008). The existence of widespread cortico-cortical projections, diverging corticospinal projections, and converging spinothalamic and cerebellothalamic afferents all have been proposed as links in a larger distributed network subserving flexibility in motor responses (Schieber 2001; Graziano 2006; Graziano and Afalo 2007; Evrard and Craig 2008). In addition, the differentially weighted ascending input originating from cerebellum and globus pallidus would be an important link in such a distributed network. The basal ganglia plays an important role in the acquisition of motor skills, the maintenance of motor routines, and procedural learning (Yin et al. 2009, for review, see Doyon et al. 2003). Both the cerebellum and the basal ganglia output nucleus, the globus pallidus, contribute to motor skill learning (Hikosaka 2002; Groenewegen 2003), but the mechanisms of how these structures interact is largely unknown. The differentially weighted thalamic output to the motor cortical areas may provide an important substrate for motor skill learning. Additional studies comparing the distributions of these projections to the motor cortical areas will help elucidate these mechanisms.

For over a decade now, the cerebellum has been increasingly implicated in cognitive processing (Schmahmann 1996; Middleton and Strick 2001; Thach 2007; Ito 2008; Strick et al. 2009). While there is wealth of neuroimaging data in humans demonstrating a role for the cerebellum in higher order cognitive processing, the precise anatomical pathways subserving such functions remain elusive based on direct anatomical tracing methods. Cerebellar inputs largely project to MI, PM subdivisions, and pre-SMA via VPLo, VLx, and VLc. Cerebellothalamic projections distribute less densely to the VA, CL and MD, nuclei that in turn project to more rostral cortical regions including eye movement related areas such as supplementary eye field, frontal eye field, and rostral part of PMd (Shook et al. 1991; Rouiller et al. 1999; Morel et al. 2005). The cerebellar input to MD is largely confined to its lateral or paralamellar portion and projections to other parts of MD are quite sparse (Stanton 1980; Kalil 1981; Asanuma et al. 1983a; Sakai et al. 1996; Stepniewska et al. 2003). Paralamellar MD and CL project diffusely to sensorimotor cortex (for review, see Jones 2007).

Since the preponderance of the cerebellar projections ultimately target premotor and motor cortical areas, it is likely that the main role of the cerebellothalamic projection system is to facilitate motor responses or action plans (see Glickstein 2007). At the same time, recent evidence suggests that prefrontal cortex may influence the motor thalamus by way of corticothalamic projections (Xiao et al. 2009), thus, providing a route for the cognitive mediation of motor plans.

## Conclusions and Future Directions

Tremendous progress has been made in detailing the cerebellothalamic and thalamocortical projections in nonhuman primates. The motor thalamus has been defined on the basis of newer chemoarchitectonic methods and correlated with the distribution and topography of these projections using a multitude of neuroanatomical tracing methods. Cerebellothalamic projections arise primarily from the contralateral dentate and interpositus nuclei and the fastigial nucleus bilaterally. These projections heavily distribute to VPLo with less dense projections to adjacent subnuclei including VLx, VLc, VLo, CL, and lateral MD. In turn, these nuclei give rise to projections to the motor cortical areas. Overall, the density of the thalamic projections to these areas varies, giving the impression that each cortical area receives differentially weighted afferents derived from the cerebellum and the globus pallidus, the second source of primary afferents of the motor thalamus. Converging input derived from the cerebellum and the globus pallidus to the motor cortical areas may provide crucial information for movement execution including motor skill learning. The thalamus occupies a pivotal position influencing cerebellar and pallidal access to the cerebral cortex but still little is known regarding the relative contributions of these structures to the overall motor network. Future studies combining multiple neuroanatomical tracers will help elucidate the details of the cortical processing of these inputs. These studies are crucial to our understanding of how motor output is influenced by ascending cerebellar and pallidal information.

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