# The role of the thalamus in motor control

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Two characteristics of the thalamus — its apparently simple relay function and its daunting multinuclear structure — have been customarily viewed as good reasons to study something else. Yet, now that many other brain regions have been explored and neurophysiologists are turning to questions of how larger circuits operate, these two characteristics are starting to seem more attractive. First, the relay nature of thalamic neurons means that recording from them, like tapping into a wire, can reveal the signals carried by specific circuits. Second, the concentration of like relay neurons into nuclei means that inactivating or stimulating them can efficiently test the functions of the circuits. Recent studies implementing these principles have revealed pathways through the thalamus that contribute to generating movements and to monitoring one's own actions (corollary discharge).

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**Abbreviations**

| | |
|---|---|
| **DBS** | deep brain stimulation |
| **EMG** | electromyograph |
| **FEF** | frontal eye field |
| **GABA** | γ-amino butyric acid |
| **GPi** | globus pallidus internal segment |
| **M1** | primary motor cortex |
| **MD** | mediodorsal |
| **MDmf** | mediodorsal nucleus pars multiformis |
| **SC** | superior colliculus |
| **SMA** | supplementary motor area |
| **VA** | ventroanterior |
| **VL** | ventrolateral |
| **VPL** | ventroposterolateral |

## Introduction

Motor control researchers argue about many issues, but for the most part they seem to tacitly agree on one point: avoid the thalamus. Figure 1a shows that the publication rate for studies on the motor thalamus has remained low and steady since 1990, in contrast to the faster pace of motor control research on areas such as the cerebral cortex, basal ganglia, and cerebellum. Moreover, only a fraction of the recent work on thalamic motor control has involved neurophysiological basic research (Figure 1b).

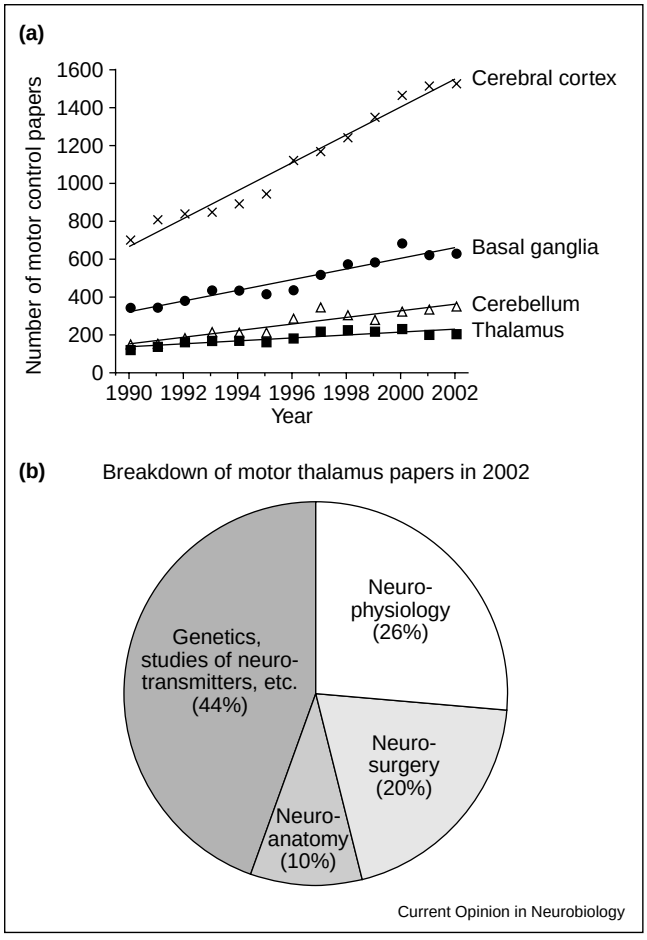
There are obvious reasons for these trends, the foremost being that the cerebral cortex, basal ganglia, and cerebellum are known to play roles in cognitive aspects of behavior [1–4]. The thalamus, by contrast, is generally considered a mere assembly of relay nodes. Its structure, too, is uninviting to the neurophysiologist, as it is parceled into multiple nuclei having irregular boundaries and only vague topographies.

There are some indications, however, that interest in the motor thalamus is growing. For example, nearly 20 years after the initial study of primate oculomotor thalamus [5,6], the first three follow-up investigations on the subject have suddenly appeared [7••,8••,9]. Recent advances in thalamic neurosurgery to relieve motor dysfunctions have inspired new lines of research, and novel neuroanatomical methods have led to a much clearer understanding of the pathways running through the thalamus [10–13]. The time is right for neurophysiologists to more thoroughly integrate their knowledge concerning motor cortex, cerebellum, and basal ganglia with the body of work established by the neurosurgeons and neuroanatomists. More than ever we are well poised to study how multiple motor-related regions work together as *circuits*, and such an endeavor necessarily leads to the thalamus.

Figure 2a shows an exploded view of the rhesus monkey thalamus. Motor thalamus has been traditionally considered to comprise two sets of anterior thalamic nuclei [14,15]. One set (Figure 2a, blue) receives input from the cerebellum and includes certain ventrolateral (VL) and ventroposterolateral (VPL) nuclei. The other set (green) receives input from the basal ganglia and includes different VL nuclei and the ventroanterior (VA) nuclei. A recently recognized third part of motor thalamus (orange) receives input from the superior colliculus (SC) and includes part of the mediodorsal (MD) nucleus [13].

Figure 2b shows in detail the pathways relayed by these thalamic regions. It is crucial to note that all of these pathways send signals from subcortical regions *up* to frontal cortex, the opposite direction to what is usually considered the 'normal' flow of information in the brain, which is from cortex downward. Pathways ascend from the cerebellum (Figure 2b, left) and the basal ganglia (middle) to nearly the entire motor-related cortex (primary motor cortex [M1], premotor cortex [PM], supplementary motor area [SMA], and frontal eye field [FEF]). The cerebellar pathway preferentially targets M1,

**Figure 1**




Publication levels of research on the role of thalamus in motor control. **(a)** Number of papers per year since 1990. Derived from PubMed using the search terms 'X' AND (motor OR movement) where 'X' was thalamus, cerebellum, basal ganglia, or cortex (slopes of the linear regressions were 8, 17, 28, and 74 papers/year, respectively). **(b)** Distribution of types of papers published on the thalamic role in motor control, for the most recent full year (2002). Neurophysiology is defined as basic research involving electrophysiology, lesions or pharmacological manipulations. Papers include original articles plus reviews and thus represent the overall interest in a subject.

whereas the basal ganglia pathway preferentially targets the SMA. The pathway originating in the superior colliculus (Figure 2b, right) targets the FEF (and perhaps other areas too, but this has not been studied in detail). In this review, recent advances in understanding these three ascending pathways through the thalamus are discussed.

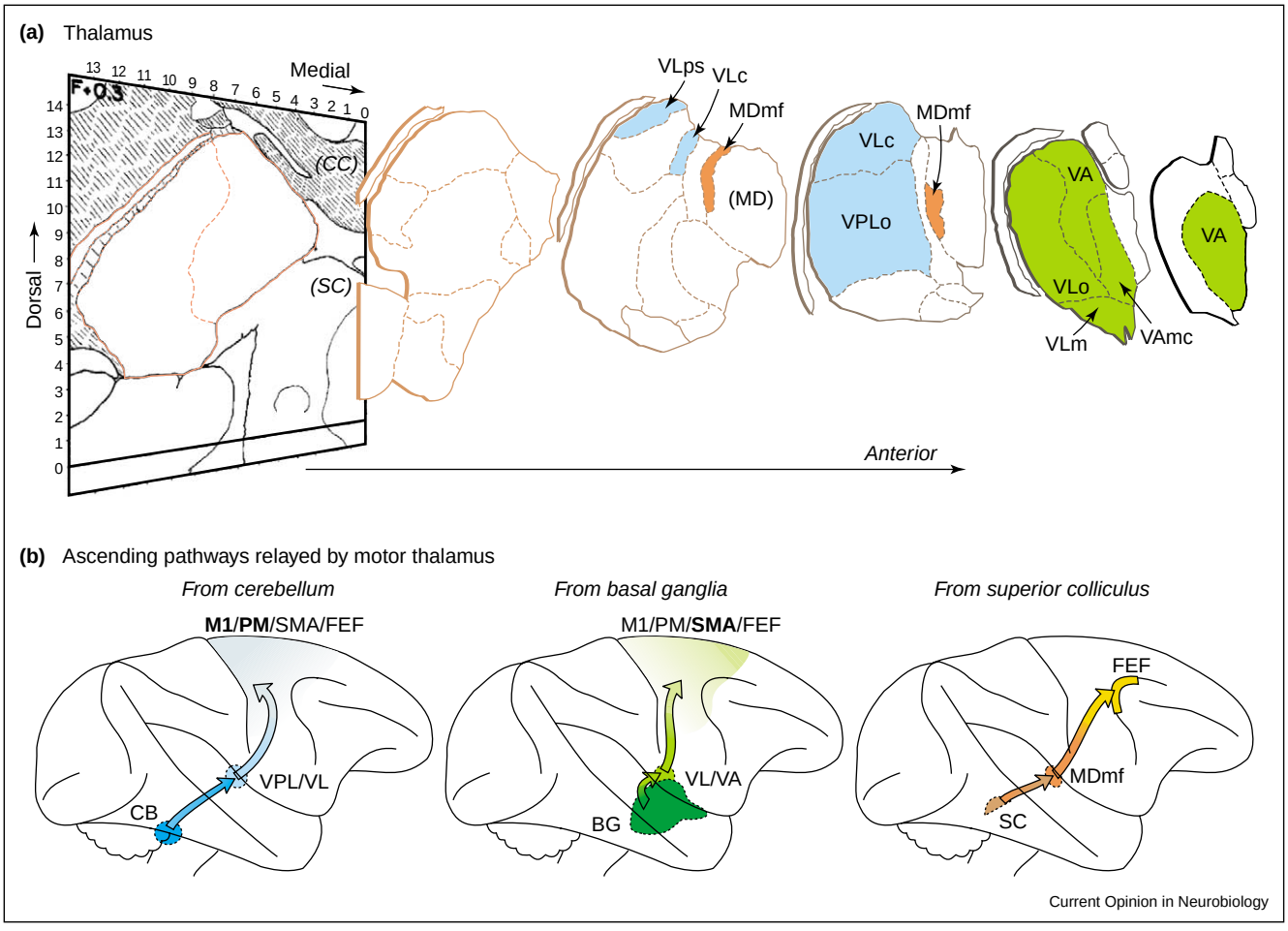
## The pathway originating in the cerebellum

Many neurons in the ventrolateral pars postrema (VLps) and caudalis (VLc) nuclei, along with the ventroposterolateral pars oralis (VPLo) nucleus (and area X, not shown in Figure 2b), receive afferents from the output nodes of the cerebellum — the dentate and interpositus nuclei [16] — and project up to the motor cortex with a bias towards M1 [17]. Research on how these neurons contribute to skeletomotor behavior extends back at least as far as the mid-1960s [18,19]. Most neurons in cerebellum-recipient thalamus have activity related both to movements and to sensory stimulation [20], and the dominant hypothesis as to the function of the cerebellar pathway through the thalamus is that it contributes to making movements in response to sensory input [16,21]. Strong support of this idea was provided in 1999 and 2000 by Van Donkelaar *et al.* [22,23], who trained monkeys to perform identical arm movements in two contexts: as dictated by a visual target ('visually triggered' movements) or as produced at will ('internally generated' movements). They found, first, that neurons in cerebellum-recipient thalamus were preferentially active during visually triggered movements, and second, that inactivating these neurons selectively impaired visually triggered movements. Since then, however, little has been published that builds upon these results.

Most of the latest studies on cerebellum-recipient thalamus have been prompted, instead, by neurosurgical issues. Carefully placed lesions of cerebellum-recipient thalamus in humans (thalamotomies) have been used since the 1950s to alleviate many forms of involuntary movements, most prominently tremors (2–11 Hz oscillations, e.g. of the hand) [10,24,25]. Since the 1980s, this has been complemented and largely supplanted by deep brain stimulation (DBS; see review by Benabid, this issue). The human nucleus targeted by these procedures, ventralis intermedius (Vim), is considered homologous to the cerebellum-recipient nuclei of the monkey [26]. A major issue stemming from the successes of thalamotomy and DBS is that we know that they work, but we do not completely understand why. If the mechanisms were better understood, this might inspire even better forms of treatment. It appears thus far that the common denominator in thalamotomy and DBS is simply the disruption of thalamic activity. In conditions of tremor, neuronal activity in cerebellum-recipient thalamus oscillates at or near the tremor frequency [27,28••,29••,30]. Thalamotomy destroys the neurons with oscillatory activity, and DBS seems to disrupt the oscillatory patterns by silencing neurons and/or by inserting activity to 'jam' or mask the signals [31•,32–34].

On a different front, recent experiments have examined the role of the cerebellum-recipient thalamus in the microstructure of movement. Although we perceive our movements as continuous and smooth, evidence is accumulating that both skeletomotor and smooth eye movements actually consist of sequential pulses that merge in time [35,36]. These discrete micromovements occur at approximately 6–10 Hz, and seem related to activity racing around a cerebello-thalamo-motor cortical-cerebellar loop [37••]. It is intriguing that this frequency range overlaps with that of the typical tremor associated with

**Figure 2**




The thalamus and the ascending motor-related pathways relayed through it. **(a)** Exploded view of the thalamus of *Macaca mulatta* from a lateral anterior viewpoint. For details see text. This schematic was constructed by digitizing summary plates from Olszewski [71], rotating them 25° back from the frontal plane, and extracting the thalamus portions of the plates. The leftmost, most posterior plate, was left intact for reference — it shows the lateral and medial nuclei of the pulvinar, topped with the reticular nucleus, along with the SC and corpus callosum (CC). Sections are 2.4 mm apart (anterior distances between sections are not to scale). Only relevant nuclei are labeled; for others see Olszewski [71]. Assignation of nuclei to the different pathways was based on two anatomical reviews [16,26] and a recent double-labeling study [17]. Olszewski data used by permission of S Karger AG, Basel. **(b)** Lateral view of the rhesus monkey brain with the anterior to the right. Three ascending pathways through motor thalamus are schematized. Abbreviations: CB, cerebellum (deep nuclei); BG, basal ganglia.

dysfunction of the cerebellar pathway (see above); it would be illuminating to test whether or not these two phenomena are related.

It should be emphasized that the term 'motor' thalamus, especially with regard to the cerebellum-recipient nuclei, does not imply complete autonomy from sensory systems. Motor thalamus sends dense projections to the somatosensory cortex [38], and cerebellum-recipient thalamic regions (although not basal ganglia-recipient regions) are innervated by somatosensory afferents from the spinal cord [39]. Inappropriate interactions between cerebellum-recipient thalamus and sensory systems may be one cause of tremor (e.g. [28••,29••,39]). Similarly, grossly abnormal receptive fields in both somatosensory cortex and thalamus occur in monkeys with focal hand dystonias; such changes in the sensory domain may contribute to this motor disorder [40].

## The pathway originating in the basal ganglia

The most anterior nuclei of the motor thalamus, the ventrolateral pars oralis and medialis (VLo and VLm) and the VA proper along with its pars magnocellularis (VAmc), receive afferents from the output nodes of the basal ganglia — the globus pallidum (internal segment) and the substantia nigra (pars reticulata) [16] — and project to the motor cortex with a bias towards the SMA [17]. Unlike both the cerebellum–motor cortex and SC–FEF pathways, which consist entirely of glutamatergic excitatory connections, the basal ganglia–motor

cortex pathway is a hybrid: the first leg to the thalamus is γ-amino butyric acid (GABA)ergic and inhibitory, whereas the second leg to the cortex is glutamatergic [14,26].

The dominant hypothesis as to the function of the basal ganglia pathway through the thalamus is that it helps to generate willful movements [16,22,23,41,42]. This seems to complement the function of the cerebellar pathway through the thalamus, which, as discussed above, helps to generate reactions to external stimuli. Neurons in basal ganglia-recipient thalamus are more apt to have purely motor-related discharges (i.e. lacking sensory responses) than those in cerebellum-recipient thalamus [20]. Moreover, neuronal activity in basal ganglia-recipient nuclei is preferentially associated with internally generated (as opposed to visually triggered) movements, and inactivating these nuclei selectively impairs internally generated movements [22,23]. The specific contribution of the basal ganglia pathway to voluntary movement generation remains controversial; a major hypothesis is that the pathway helps to select which movement to make when multiple alternatives are possible (e.g. [43,44••]).

The conclusion that the basal ganglia pathway is important for willful movements is supported by the well known symptoms of Parkinson's disease, in which basal ganglia circuits are disrupted and voluntary movements diminish or disappear. The preferred targets of neurosurgery to treat paucity of movement are the basal ganglia nuclei themselves (e.g. subthalamic nucleus), but to relieve Parkinsonian tremor or rigidity it can be effective to target the basal ganglia-recipient thalamic nuclei (human areas ventralis oralis anterior, Voa, or posterior Vop) [10,45]. Neurons in the basal ganglia-recipient thalamus exhibit abnormal activity (oscillating and/or elevated firing rates) during involuntary movements, and thalamotomy/DBS is thought to reduce tremor and rigidity by disrupting this activity [28••,46•,47]. Intriguingly, lesions or DBS in the cerebellum-recipient Vim also relieve Parkinsonian tremor [10,45,48], which suggests that the cerebellar and basal ganglia pathways are not independent of each other but interact at some level, for example in the cortex.

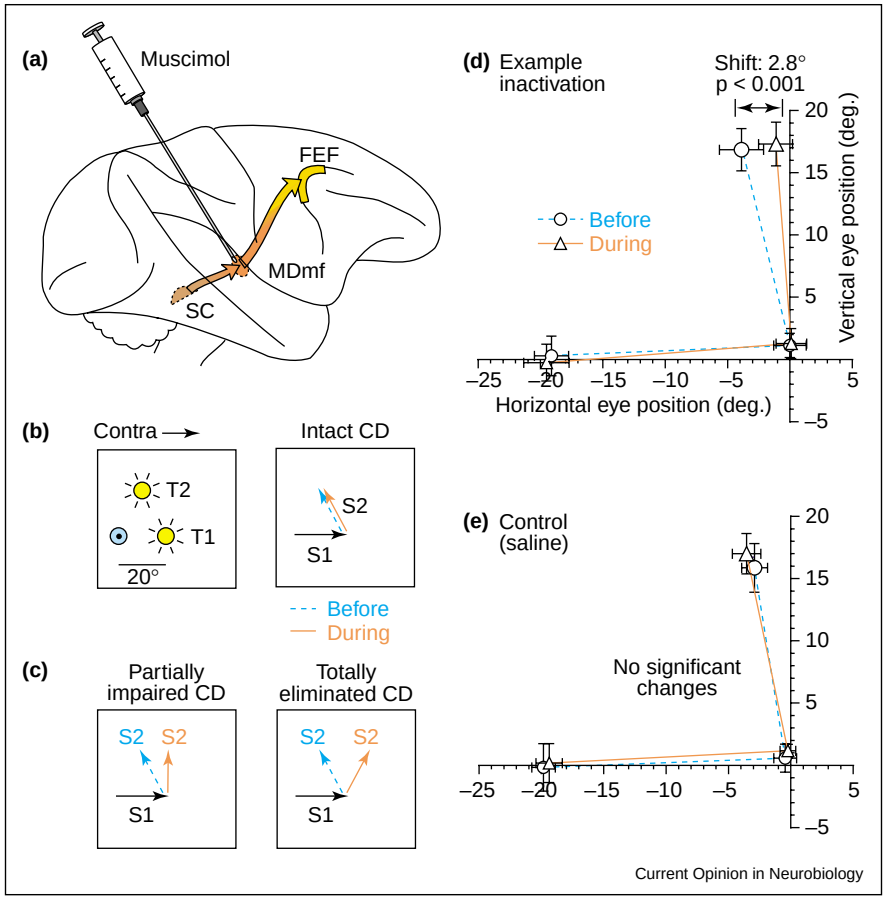
Further indications that the ascending pathways through the motor thalamus are more complicated than originally thought have been provided by recent neuroanatomical work. McFarland and Haber [49] showed, for example, that thalamic nuclei associated with the basal ganglia form intricate connections with various frontal lobe regions; in addition to transmitting basal ganglia output to motor cortex, these nuclei also may transfer information between cortical areas. Another study [50] focusing on M1 demonstrated that it receives input from more extensive regions of the thalamus than previously appreciated, and that it sends to the thalamus multiple types of projections (having varying sizes of terminal fields and synaptic boutons). These anatomical findings are similar to recent results from the sensory domain that have inspired two influential hypotheses: first, that the thalamus aids in cortico–cortical communication and second, that it receives two differing kinds of projections ('drivers' versus 'modulators') from the cortex [51–53]. Much more neurophysiological research is needed to test these hypotheses, especially as they pertain to motor cortex and thalamus.

## The pathway originating in the superior colliculus

A third pathway, involved in eye movements, has recently been confirmed as ascending through motor thalamus [13]. Many neurons at the lateral edge of the mediodorsal nucleus, apparently in pars multiformis (MDmf), receive input from the saccade-related intermediate layers of the SC and project, in turn, up to the FEF. The first investigation of eye-related neuronal activity in or near MDmf [5,6] found a variety of signals including spatially tuned visual responses and bursts of presaccadic activity. Two laboratories recently returned to this general thalamic region and found, in addition to the signals described previously, activity related to more cognitive aspects of behavior [7••,8••]. This activity occurs after visual stimulation and before saccade generation and may be related to processes of working memory or movement preparation [54,55]. In summary, it has been well established that the general population of neurons in the MDmf region is active during many aspects of oculomotor behavior.

Robert Wurtz and I set out to study the SC–FEF pathway in more detail by finding and characterizing the specific MD neurons that relay signals from SC to FEF [9]. We physiologically identified MD relay neurons by orthodromically activating (synaptically driving) them from the SC and antidromically activating (backfiring) them from the FEF. They were clustered, as expected, in lateral MD (presumed MDmf). Most had spatially tuned presaccadic activity, and because we knew from our physiological identification that this activity traveled from the SC up to the frontal cortex — away from the saccade generating circuits of the pons and midbrain — we hypothesized that the activity represented corollary discharge, that is, internal information about saccades. To test this idea we inactivated MD relay neurons with the $GABA_A$ agonist muscimol while monkeys performed a task that required the use of corollary discharge. Figure 3 summarizes the result: inactivation impaired corollary discharge about saccades but spared the ability to generate saccades. Our recording and inactivation findings therefore indicate that a major function of the SC-MD-FEF pathway is to convey corollary discharge (for critical evaluation of this study by others, see [56,57]). This corollary discharge contributes to coordinating sequential saccades and may help to stabilize the perceived visual scene across saccades by warning the visual system about imminent retinal rotations [58,59].

**Figure 3**




Evidence that the SC-MD-FEF pathway plays a role in corollary discharge (CD). **(a)** It was known from recording experiments that saccade-related activity, hypothesized to act as CD, courses from SC up to FEF. We interrupted transmission of this activity by injecting muscimol at the sites of MD relay neurons. **(b)** Monkeys performed a double-step saccade task. Left: each trial started with the monkey foveating a spot (dot in blue circle). Then two targets, T1 and T2, were flashed briefly. The monkey's task was to make sequential saccades in darkness to the target locations. Right: a first saccade (S1) is made to the T1 location. If CD about S1 is available, the monkey will know that S1 was made correctly and thus will make an accurate, leftward diagonal second saccade (S2) to reach the T2 location. An unchanged S2 during versus before inactivation indicates, therefore, that CD is intact. **(c)** Indications that CD is impaired. Left: partial impairment of CD would cause the monkey to misjudge the vector of S1. Impaired CD may indicate that S1 was shorter than it actually was, for example, causing the monkey to make a more vertical S2 to compensate. As S1 is actually normal, S2 will land further to the right during inactivation than before. Right: total elimination of CD would cause the monkey to think it failed to make an S1 (even though S1 was actually normal). If the monkey tries to finish the trial by looking at the T2 location, the end result will be that S2 travels diagonally rightward. In summary, *the worse the CD impairment, the larger the rightward shift in S2 endpoints.* **(d)** Sample data from an inactivation experiment. The monkey's second saccade endpoints shifted to the right, consistent with partially impaired CD. There were no other significant changes. Symbols show means and SDs of around 20 trials. **(e)** Sample data from a control injection of saline; there were no significant effects. These sample data are representative of results from two monkeys and multiple injections [70].

## Conclusions

Although we are still at an early stage of understanding the role of thalamus in motor control, important progress has been made in the past few years. It is becoming clear that the relay nature of the motor thalamus is far from a boring feature — rather, it is an experimental gift that allows us to eavesdrop on what subcortical regions tell the frontal cortex. And although the thalamus may appear to be a maddening jumble of nuclei, a proven strategy for dealing with this in recording studies has been to rely less on anatomically localizing thalamic neurons and more on physiologically identifying them as belonging to particular pathways using anti- and orthodromic stimulation (e.g. [9,60]). Once identified with anatomical and/or physiological methods, local concentrations of thalamic relay neurons can be efficiently inactivated or stimulated to perturb specific pathways (e.g. [9,10,23]). Applying these strategies, recent studies have provided insight into the previously mysterious ascending motor pathways of the brain.

This review leads, in my opinion, to three main conclusions regarding future research. First, important lessons have been learned from studying how motor thalamus mediates arm movements, and these should be kept in

mind when planning future studies exploring how the motor thalamus mediates eye movements. As is summarized in Figure 2b, the cerebellar and basal ganglia pathways relayed by the motor thalamus target the FEF in addition to the other frontal cortex motor areas. Future studies should physiologically identify thalamic relay neurons of the cerebellum–FEF and basal ganglia–FEF pathways and examine whether their activity is preferentially associated with visually triggered or internally generated eye movements, respectively, as was found for arm movements. It would greatly strengthen the general principle that the two pathways perform these distinct functions if the skeletomotor results were replicated in the oculomotor domain.

Second, we also learned an important lesson from studying oculomotor thalamus that should be kept in mind when planning future skeletomotor studies. The finding that corollary discharge of eye movements is conveyed from SC up to the FEF through MD thalamus begs the question, is corollary discharge of skeletal movements sent from any subcortical area up to the frontal cortex through VL, VPL, or VA thalamus? Corollary discharges of arm, wrist, and finger movements are thought to play important roles in behavior (e.g. [61,62,63,64•]), but the circuits that carry these discharges remain unknown. A promising hypothesis is that some of these circuits ascend through the motor thalamus.

Finally, an assumption throughout this review has been that the motor thalamus acts as a passive relay. It is possible, however, that to some extent the motor thalamus modifies the signals that pass through it. Current hypotheses that the thalamus acts as more than a relay station have been based mostly on anatomical data and studies of sensory thalamus (e.g. [52,65]). Concrete physiological assessments of the extent to which signals change en route through the motor thalamus are still needed.

## Update

Five papers published very recently are also relevant. First, Kelly and Strick [66] used a combination of retro- and anterograde viral tracing methods to provide the strongest neuroanatomical evidence yet that the pathway from cerebellum through thalamus to motor cortex forms a closed loop. Second, MacMillan *et al.* [67] succeeded in recording from human motor thalamus while neurosurgical patients performed visually triggered versus internally generated (remembered) sequences of button presses. As expected from prior data discussed in this review, neurons responding selectively for internally generated movements were localized to basal ganglia-recipient thalamus. They found no spatial localization of neurons selective for visually triggered movements, however. Third, a psychophysical experiment by Tanaka [68] provided new evidence that much of the corollary discharge used for planning second saccades in the double-step task arises from below the SC, presumably traveling from deep brainstem to thalamus to cerebral cortex (through pathways as yet unknown). This may explain why inactivating the SC-MD-FEF pathway causes only partial deficits in the double-step task (Figure 3). Finally, we published a pair of papers describing in detail our recording and inactivation studies of the SC-MD-FEF pathway [69,70]. One result of the recording study [69] is relevant to the final conclusion point I make above, concerning whether motor thalamus neurons modify the signals that they relay to the cortex. We found evidence that MD relay neurons faithfully transmit high-frequency, phasic bursts of activity but largely filter out low-frequency, tonic activity.

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