The Role of the Corticothalamic Projection in the Primate Motor Thalamus

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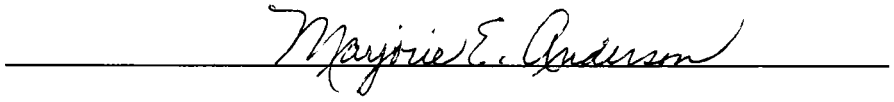

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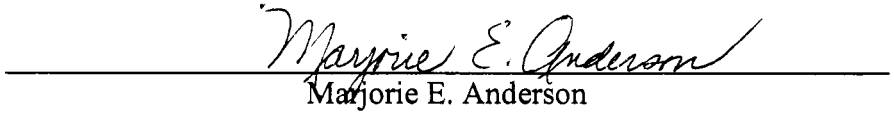

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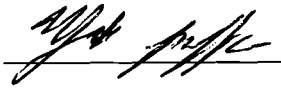
Signature 

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Abstract

The Role of the Corticothalamic Projection in the Primate Motor Thalamus

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The work in this dissertation focuses on identifying corticothalamic neurons and characterizing the signals carried along this pathway in the primate motor system. All experiments were carried out in awake primates performing a visually-guided center-out reaching task. We used stimulation in the motor thalamus (VPLo) to antidromically and orthodromically activate neurons in the primary motor cortex. Cortical neurons that showed antidromic responses to thalamic stimulation were classified as corticothalamic neurons (CT), while those that showed orthodromic responses were considered to be recipients of information from the stimulated area of thalamus. We also recorded the neural activity of thalamic neurons near the stimulation sites.

We identified two distinct populations of CT neurons. The "inactive" population had virtually no spontaneous or task-related neural activity, while the "active" population showed task related activity typical of M1 pyramidal neurons. "Inactive" neurons typically exhibited long latencies and high thresholds to stimulation and were found deep within recording tracks, while "active' neurons had shorter latencies and lower thresholds to stimulation and were located more superficially in a recording track. We presumed that the "active" neurons are CT neurons that originate in cortical layer V and that the "inactive" neurons are layer VI CT neurons.

We compared the neural activity of potentially connected groups of cortical and thalamic neurons. Corticothalamic neurons and the thalamic neurons located near the stimulation site from which those CT neurons were antidromically activated were grouped into CT sets and cortical neurons that showed orthodromic activation were grouped with thalamic neurons as part of TC sets. Based on the stimulation responses and narrow dispersion of preferred directions we proposed that these sets of neurons are potentially connected. Cortical neurons in both types of sets showed more sharply tuned directional responses than thalamic neurons in the same sets. Cortical neurons in CT sets modulated their activity earlier in relation to the onset of movement when compared with the thalamic neurons in the same sets and the cortical neurons in the TC sets.

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Chapter I

General Introduction

The thalamus has traditionally been considered the major relay station for information on its way to the cerebral cortex; however it is becoming clear that it also plays substantial roles in processing and integrating incoming sensory information, mediating cortico-cortico communication and regulating the ability of cortex to process incoming information. Many of these more expansive thalamic functions are dependent on the interconnections between cortex and thalamus, yet the corticothalamic component of this circuit remains understudied. The work in this dissertation focuses on identifying corticothalamic neurons and characterizing the signals carried along this pathway in the primate motor system.

The thalamus is the largest, most internal structure of the diencephalon, located at the rostral end of the midbrain on each side of the third ventricle. It is divided into a dorsal and a ventral component. The dorsal thalamus is composed of numerous topographically organized nuclei that reciprocally project to limbic, sensory, and motor regions of the cerebral neocortex. Situated along the ventral and lateral surface of the dorsal thalamus is the reticular nucleus, the primarily component of the ventral thalamus, (Jones, 1985).

In mammals, almost all ascending information is communicated to cerebral cortex through thalamus, and the functions of major neocortical regions are defined by their inputs from the nuclei of the dorsal thalamus. For example, visual cortex has a visual function because it receives visual input through the lateral geniculate nucleus (LGN), the thalamic relay of information from the retina. Many studies on the thalamus have involved the projections of retinal ganglion cells onto the LGN and then to visual cortex, and much of our knowledge of anatomical and physiological thalamic organization derives from that system. Because studies on other areas of thalamus have been shown to have organizations similar to that found in the LGN, the visual system is a useful model for the overall thalamus.

In the LGN, retinal inputs are distinguished by large axons producing very large terminals and synapses. These synapses are powerful, activate only ionotropic receptors, and show activity dependent depression. Although this excitatory glutamatergic retinogeniculate projection is considered the driving input to LGN, it is far from being the largest input, contributing only 5-15% of the synaptic input to the relay cells (Erisir et al., 1997a; Van Horn et al., 2000). Instead, the most numerous synapses come from corticothalamic neurons, which provide about 50% of the synapses on relay cells in LGN (Katz, 1987; Sherman and Koch, 1990). These corticothalamic axons originate primarily from layer VI in the same cortical area that is innervated by the thalamic nucleus in question, visual cortex in the case of the LGN (Jones, 1985).

There are also a small number of afferents from brainstem areas, including cholinergic afferents from the parabrachial region, noradrenergic axons from the locus coeruleus and serotonergic axons from the dorsal raphe. These brainstem inputs can be either excitatory or inhibitory (Ohara et al., 1983; Bickford et al., 1993; Bickford et al., 1994; Gunluk et al., 1994; Erisir et al., 1997b; Sherman and Guillery, 2006). A generalized schematic of this thalamic circuitry is shown in Figure 1.1.

The basic information relayed by the LGN in the form of receptive field properties is provided by retinal inputs, since these have the same center/surround receptive fields as do relay cell receptive fields (Hoffmann et al., 1972). This is not the case for the layer VI corticothalamic and brainstem inputs, and this has led to the idea that these inputs can be functionally divided into drivers and modulators (Sherman and Guillery, 1998, 2006). The drivers represent the main information to be relayed, and the modulators modify the relayed information.

The function of a thalamic nucleus is thus largely defined by its driver input. In addition to the geniculate relay cells being defined by their retinal inputs, those of the ventral posterior nucleus are defined by their medial lemniscal inputs and those of the ventral portion of the medial geniculate nucleus by their auditory inputs. (Sherman and Guillery, 2006) According to the model proposed by Guillery and Sherman, these thalamic nuclei, driven by sensory afferents, are considered first-order thalamic relays (Guillery and Sherman, 2002a). However, in thalamic nuclei not dominated by sensory

afferents, or 'higher-order relays', the driving inputs may include a layer V corticothalamic projection. This layer V input is equivalent to the retinal input to the LGN with regard to many morphological features, and it is proposed to act as a driver input important for cortico-thalamo-cortico relay of information (Guillery, 1995; Sherman and Guillery, 2006). Examples of higher-order relays associated with sensory systems include the pulvinar for the visual system and the dorsal division of the MGN for the auditory system.

The size and nature of the corticothalamic pathway underscores its importance to thalamic circuitry, yet it has remained relatively understudied. The corticothalamic neurons that innervate the thalamus are located in both layer V and layer VI of cortex. As we have seen, the layer VI projection is thought to act as a modulator of thalamic activity, and it has been proposed that the layer V projection plays a role in cortico-cortico communication via the thalamus (Guillery and Sherman, 2002a). However, not all thalamic nuclei fall clearly into the first-order and higher-order categories of Guillery and Sherman, and evidence for the roles of the different corticothalamic projections comes mostly from the visual system. In particular, the motor thalamus stands out as an exception to this model, and studies of the corticothalamic projection to the motor thalamus are very limited.

General features of the corticothalamic projections

Layer V corticothalamic projection

In general, layer V corticothalamic (CT) cells are large pyramidal cells that send myelinated axons back to the same nuclei in the thalamus that project to that part of cortex, but in a diffuse manner. The Layer V projections to the thalamus are collaterals of axons projecting to brainstem and beyond (Sherman and Koch, 1990; Levesque et al., 1996; Pare and Smith, 1996). The pattern of axonal branching is broad, with richly branched arbors, ending in large terminals. Layer V terminals are located on the proximal dendrites, ending in large boutons, and associated with ionotropic receptors. (Wilson et al., 1984; Vidnyanszky and Hamori, 1994; Erisir et al., 1997b; Rouiller et al., 1999; Rouiller and Welker, 2000). Occasionally these terminals are part of a structure called a triad or glomerulus. In LGN of cat, it has been shown that the glomerulus structure includes driving input terminals, interneuron presynaptic dendrites, and sometimes brainstem projection terminals. Glomeruli are less common in primate thalamus, but they still are found. The role of triads and glomeruli is unclear (Peschanski et al., 1983). No terminals of layer V axons are found in thalamic reticular nucleus (TRN) (Ilinsky et al., 1997; Ilinsky and Kultas-Ilinsky, 2002).

The structure and synaptic relationships of these corticothalamic terminals have been demonstrated by electron microscopy for axons arising in somatosensory cortex

(Hoogland et al., 1991), visual cortex (Mathers, 1972; Ogren and Hendrickson, 1979; Feig and Harting, 1998), auditory cortex (Bartlett et al., 2000), and frontal cortex (Schwartz et al., 1991); and light microscopic studies of individual axons have demonstrated their cortical origin from layer V and their characteristic terminal structure for axons from somatosensory (Bourassa et al., 1995), visual (Vidnyanszky and Hamori, 1994; Bourassa and Deschenes, 1995), and auditory cortex (Rouiller and Welker, 1991; Ojima, 1994).

Layer VI corticothalamic projection

A highly specific reciprocal connection exists between thalamus and Layer VI CT neurons, which make up about 50% of the layer VI cells (Updyke, 1977; Berson and Graybiel, 1983). The layer VI CT neurons are small and have unmyelinated axons that project to interneurons and distal dendrites of relay neurons in the thalamus, where their terminals are small (Swadlow, 1994). They also send collateral projections to the TRN and to other cortical neurons in Layers III and IV (Katz, 1987). Layer VI axons contact many thalamic relay neurons, but it is likely that these multiple relay cells have closely matched receptive fields (Sanderson, 1971; Sanderson and Sherman, 1971). The layer VI corticothalamic projections are glutamatergic (Montero, 1994), terminating on both ionotropic and metabotropic receptors (McCormick and von Krosigk, 1992).

Functional knowledge of CT neurons

In studies of cortical efferents in the rabbit, Swadlow characterized some of the properties of both layer V and layer VI CT neurons, defined by their antidromically-conducted spikes evoked by stimulation in the thalamus (Swadlow et al., 1978; Swadlow, 1988, 1989, 1990, 1991). Swadlow found that in multiple areas of awake rabbit cortex (S1, S2, V1, and M1) the properties of these neurons remained consistent within layers, but had substantially different properties across layers. Layer V neurons were found to have high conduction velocities (mean = 12.76 m/s), large receptive fields (> 25 hairs in somatosensory cortex), and a mean spontaneous firing rate of 4.1 spikes/second. The layer VI CT cells had low conduction velocities (mean 1.96 m/s), smaller receptive fields (< 14 hairs) and a low mean spontaneous firing rate of < 1 spike/second.

Motor thalamus

The motor nuclei of the thalamus (VPLo, VLo, VA) have patterns of inputs and outputs that differ slightly from either a first-order sensory relay nucleus such as LGN or a higher-order nucleus such as pulvinar. Importantly, motor nuclei potentially

receive dual driving inputs from the basal ganglia or cerebellum, and from a layer V corticothalamic projection.

Neurons in the cerebellar receiving nucleus of the thalamus (VPLo) receive excitatory afferents from the output nuclei of the cerebellum, the dentate and interpositus nuclei (Tracey et al., 1980; Kalil, 1981; Asanuma et al., 1983; Ilinsky et al., 1987; Middleton and Strick, 2000), and project to the motor cortex with a strong bias towards M1 (Dum et al., 2002; Sakai et al., 2002). The incoming cerebellar fibers to thalamus form large secure synapses on proximal dendrites of thalamic relay cells (Sakai et al., 1996). The ultrastructure of these synapses suggests a highly secure transmission line, a notion supported by electrophysiological studies that show large EPSPs in response to a single stimulation pulse in the cerebellum (Uno et al., 1970; Shinoda et al., 1985). Microstimulation of focal sites in deep cerebellar nuclei causes short-latency increases in discharge in M1 neurons and reciprocal facilitation and suppression in averages of antagonistic muscle electromyograms, further demonstrating the strength of the cerebello-thalamo-cortical pathway (Holdefer et al., 2000) and strongly suggesting that cerebellar input acts as a driving input to motor thalamus.

In their anatomical studies, Ilinsky and Kultas-Ilinsky have analyzed the ultrastructure of the thalamic motor areas in monkey (Kultas-Ilinsky et al., 1980; Ilinsky and Kultas-Ilinsky, 1984; Kultas-Ilinsky and Ilinsky, 1991). Their results show that the structure of this portion of the thalamus in monkey is consistent with the structure of

LGN and other thalamic nuclei studied in cat and rat. Two types of neurons are found in motor thalamus: GABAergic interneurons with large dendritic trees, and medium sized projection neurons having a dendritic tree displaying a tufted branching pattern. Corticothalamic axons contribute numerous small terminals (SR), containing round vesicles that make asymmetric contacts primarily on the distal dendrites. These are labeled by injection of WGA-HRP in motor and premotor cortices. Larger terminals (LR), also containing round vesicles, make asymmetric contacts onto proximal dendrites and are labeled by injection of WGA-HRP in motor cortex. The cellular organization was found to be in a clustered pattern, with many projection neurons grouped together with one or two interneurons associated with each cluster (Ilinsky et al., 1997; Kultas-Ilinsky et al., 1997).

The relationship between cortical laminar origin and axonal termination was established in cat motor cortex by reconstructing the morphology of single axons labeled with fine focal injections in cat M1. This revealed that the small Type 1 endings are associated with corticothalamic neurons originating in Layer VI, while the axons with giant Type II endings arise from Layer V (Kakei et al., 2001). The same study showed that the Layer VI projections gave off collaterals to the thalamic reticular nucleus, while the Layer V projections did not. This laminar pattern has also been demonstrated in the S1 and prefrontal cortex of monkey, the cat primary auditory cortex, and the rat S1 and primary visual cortex (Rouiller and Welker, 2000).

In summary, the cerebellar receiving area of thalamus has the same general circuitry and anatomical characteristics as other thalamic areas. Anatomical and electrophysiological studies show that the cerebello-thalamic projection is the driving input to this part of motor thalamus. Finally, there is a dual layer V/VI corticothalamic projection from motor cortex. The presence of a substantial layer V corticothalamic input as well as the subcortical driving input from cerebellum makes the cerebellar receiving thalamus different from most other thalamic nuclei, and an intriguing subject for studying the role of the corticothalamic projection.

Functional roles for the corticothalamic projections

A review of the literature reveals a number of proposals for the functional roles of the corticothalamic projections, but many of these are based on studies with limited breadth that may not generalize well to all thalamic nuclei. As described above, anatomical studies have shown that the dual morphological nature of the corticothalamic projection, arising from layers V and VI, is common across different thalamic nuclei and across a number of different species. The dichotomy of the structure and synaptic relationships of these corticothalamic projections also strongly suggests that these two populations have very different functional roles.

Proposed roles for the Layer V corticothalamic projection

The Layer V corticothalamic projection, as reviewed above, is made up of pyramidal cells that send myelinated branches of axons to thalamus that terminate in large boutons on proximal dendrites and activate ionotropic receptors. This collection of characteristics implies a function that includes the rapid and secure transmission of a copy of cortical output to the thalamus. These neurons also share these features with known drivers of thalamic activity, such as the retinogeniculate projection. Collectively, this evidence suggests that the layer V CT projection is ideally suited to strongly influence and perhaps act as the primary driver of thalamic activity.

There is some physiological evidence that layer V CT input provides a driving type input to thalamus, particularly to motor areas of thalamus. A series of studies that analyzed the activity of antidromically-identified potential corticothalamic neurons in the rabbit and cat motor cortices during postural corrections or locomotion (Beloozerova and Sirota, 2003; Beloozerova et al., 2003a; Beloozerova et al., 2003b; Beloozerova et al., 2003c; Sirota et al., 2005) showed that potential corticothalamic neurons from layer V were strongly activated during postural corrections or a complex stepping behavior. This showed that the layer V neurons carried a potential, task-related, driving input to thalamus. However, the researchers did not analyze the activity of thalamic neurons, so it is still unknown how this input affected thalamic activity. Additionally, the tasks used in these studies, postural correction and stepping, can occur

without cortical input and as such, may not be strong drivers of the corticothalamic projection.

Another study focusing on the basal ganglia receiving areas of thalamus also suggests a role for the CT projection as a driving input. The corticothalamic input to the basal ganglia receiving areas of thalamus provide the only known excitatory input to this area. Two observations make this corticothalamic input to the basal ganglia of special interest. First, in spite of the high-frequency tonic inhibition that basal ganglia receiving neurons receive from GPi or SNr, their "resting" activity in awake monkeys is indistinguishable from that of cerebellar receiving neurons, which receive high frequency tonic excitation from deep cerebellar nuclei (Anderson and Turner, 1991). Second, when the inhibitory output of the pallidus is suppressed by a muscimol injection, thalamic neurons in the PR show an increase in tonic activity consistent with removal of inhibition, but they still show task modulated activity (Inase et al., 1996). Corticothalamic fibers are the most probable candidate to be the source of this task-related phasic signal.

Guillery and Sherman have proposed an additional role for layer V CT neurons in cortico-thalamo-cortico communication. They suggest that higher-order relays send information already in cortex via layer V CT driver input from one cortical area to the middle layers of another cortical area. This proposal is based primarily on anatomical studies of the pulvinar and its connections with cortical areas. There are significant

layer V cortical inputs from areas V1 and V2 to pulvinar, but there is only a weak reciprocal thalamocortical projection back to cortex. Instead, the region of the pulvinar that receives input from V1 has a major projection to V2, and the V2 recipient pulvinar has a major projection to V4. Thus, the cortico-pulvinar-cortical projections appear to relay information from one area of cortex to another and mirror the direct cortico-cortical connections. This connectivity has led to the proposal that this pathway is an important component of cortical-cortical communication (Guillery and Sherman, 2002a; Shipp, 2003).

Most recently, Sherman and Guillery have also proposed a role for the thalamus as a monitor of motor output. They suggest that cortical efferent messages contain information that ultimately contributes to motor output, and that an efferent copy is carried to the thalamus by the layer V corticothalamic projection. Furthermore, they argue that current evidence indicates that many and possibly all thalamic relays to the cortex are about instructions that cortical and subcortical neurons are contributing to movement control (Guillery and Sherman, 2002b). Recent studies have lent some support to this proposal by showing that the projection from the superior colliculus (SC) to the mediodorsal thalamus (MD) carries a corollary discharge of the oculomotor command (Sommer and Wurtz, 2004a, b).

Proposed roles for the layer VI corticothalamic projection

Layer VI terminals are well suited to have modulatory and long-term effects on relay neurons. The metabotropic receptor associated with Layer VI neurons produces a slow, long lasting EPSP caused by a reduction of K^+ leak current (McCormick and von Krosigk, 1992). The depolarization that results may drive the relay neuron from a hyperpolarized bursting state to the more depolarized tonic response state. The location of the many small bouton terminations on distal dendrites is also consistent with a modulatory role. From the more distal location, activity of these layer VI terminals can control the membrane potential of the dendritic tree but have little effect on the potential at the soma. This arrangement might allow Layer VI activity to modulate the driving activity to the relay cell by changing membrane potential in the dendrites, thereby changing the response mode of thalamic relay neurons.

The conductance underlying the rhythmic bursting type of activity is the I_T current. Once activated, the I_T conductance produces recurrent low threshold Ca^+ spikes. In this mode, relay cells respond to stimuli in a non-linear fashion; an all-or-nothing response. When a sufficient stimulus is presented, the relay cell fires with a rhythmic burst of low threshold spikes, irrespective of the magnitude of the stimulus. This may seem like a poor way to relay a signal to cortex, since all information coded in the modulation of that signal is lost in this all-or-none response (Contreras and Steriade,

1995; Steriade and Contreras, 1995; Contreras et al., 1996). The advantage of this response mode is that it has a much higher sensitivity to stimuli than the tonic mode and has a much higher signal-to-noise ratio. Even a very small EPSP can elicit a response from a relay cell, because the low threshold conductance is activated (Guido et al., 1992; Guido and Weyand, 1995).

When the I_T current is not activated, thalamic neurons fire with a tonic pattern that is linearly related to the synaptic input received. This response mode retains all the information in an incoming signal and passes it on to the cortex. It is in this response mode that the most effective relay of information is accomplished (Guido et al., 1995).

The layer VI corticothalamic feedback potentially modulates the response properties of thalamic cells in a push–pull arrangement (Sherman and Guillery, 2002). Cortical feedback appears to promote focal switching from burst- to tonic-firing modes in thalamic relay cells (Funke and Eysel, 1992) via the prolonged depolarization caused by mGluR1-type metabotropic receptor activation (McCormick and von Krosigk, 1992; Rivadulla et al., 2002). The axons of thalamic reticular nucleus cells, which are also excited by corticogeniculate axons, induce prolonged hyperpolarization via GABA-B metabotropic receptors (Kim and Vezina, 1997). Thus, top–down corticothalamic feedback can alter the spatiotemporal response properties of thalamic cells through monosynaptic excitation and disynaptic inhibition.

There are some studies that demonstrate the effects that layer VI corticothalamic feedback may have on the flow of sensory information to cerebral cortex (Sherman and Guillery, 2002). Corticothalamic feedback has been found to improve the spatiotemporal coherence between cortex and thalamus (Sillito et al., 1994; Contreras et al., 1996), with the strength of feedback able to control the frequency of thalamic oscillatory activity (Bal et al., 2000). In the visual system, focal corticogeniculate feedback appears to provide motion-directional contextual modulation of thalamic receptive-field properties (Sillito et al., 1994; Grieve and Sillito, 1995; Murphy and Sillito, 1996; Sillito and Jones, 2002). In the motor system, layer VI corticothalamic neurons have been shown to have very low rates of activity during postural corrections and stepping tasks in rabbits and cats, but to date there is no evidence supporting their role as a modulator of thalamic neurons in the motor system.

What role do corticothalamic neurons play in the motor system?

The signals carried by corticothalamic neurons in the monkey, and especially during visually targeted reaching movements, remain unknown. Despite the recent studies investigating the layer V and VI corticothalamic projections reviewed here, only a small amount of data has been collected relating to the corticothalamic projection in the motor system. While stepping and stumbling, as studied in the cat and rabbit, can occur without suprapinal input (Whelan, 1996), the activity transmitted from the cortex

to thalamus via neurons in either layer V or VI could be quite different during a reaching movement. Additionally, while some studies of the corticothalamic projection utilized stimulation techniques to identify corticothalamic neurons, very few attempted to correlate the activity of corticothalamic neurons with that of the recipient neurons in the thalamus. Sommer and Wurtz (Sommer and Wurtz, 2004a, b) have recently used a variety of stimulation and recording techniques to identify and record from neurons along the pathway from the superior colliculus to the frontal eye fields via the mediodorsal thalamus. This allowed them to begin to characterize the contribution of a specific input to the activity of thalamic and cortical neurons. The objective of this dissertation is to determine the signals carried by primate corticothalamic neurons and then to examine how this activity might shape the activity of thalamocortical cells and of other neurons in the motor cortex.

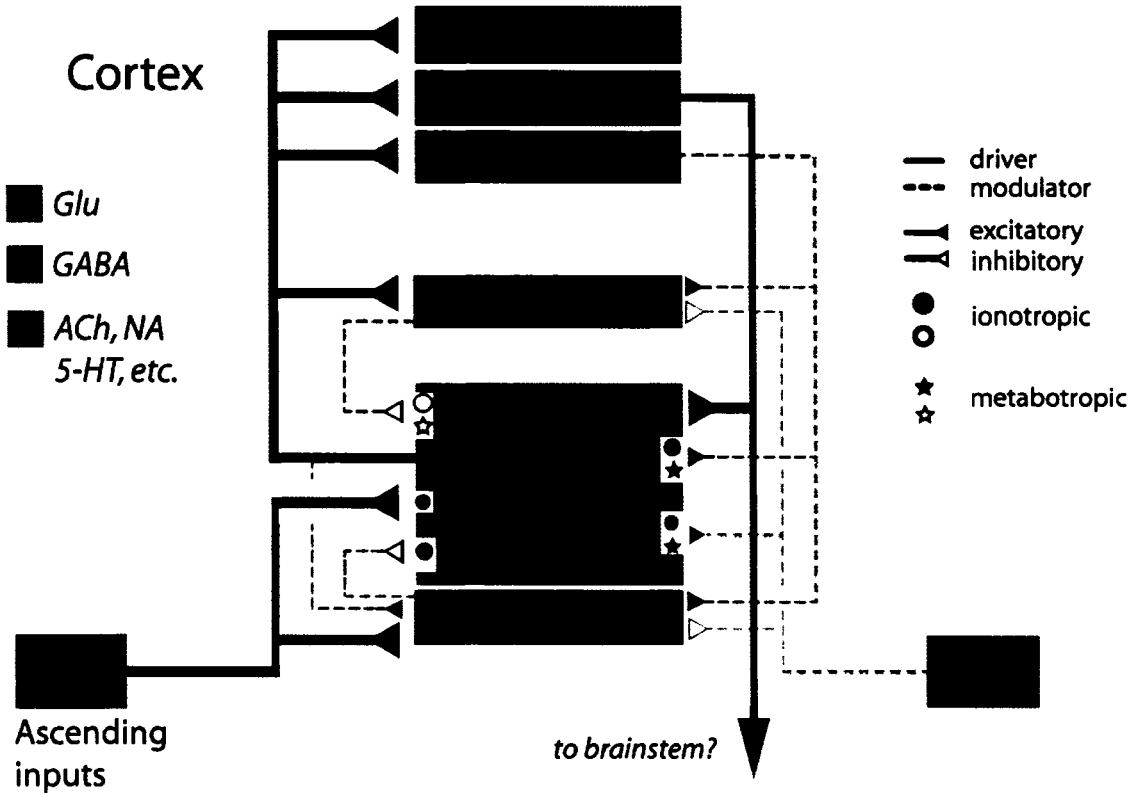

Figure 1.1: Schematic diagram of the generalized circuitry for thalamic nuclei. The inputs to relay cells are shown along with the relevant neurotransmitters and postsynaptic receptors (ionotropic and metabotropic) Abbreviations: BRF, brainstem reticular formation; TRN, thalamic reticular nucleus.

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Chapter II

Characterization of the Corticothalamic Projection in the Primate Motor System

Introduction

As the major gateways to the cerebral cortex, thalamic nuclei receive substantive inputs from subcortical structures, including sensory nuclei in the visual, auditory, somatosensory systems and motor-related structures, such as the basal ganglia and the dentate nucleus of the cerebellum (Jones, 1985). Emotional or motivational data from the amygdala and the mammillary body also pass through the thalamus (Novotny, 1977). These inputs are largely excitatory, with the exception of those from the two basal ganglia output nuclei, the internal globus pallidus and the pars reticulata of the substantia nigra.

Often neglected is the fact that all thalamocortical projections are reciprocated by feedback projections from cortex to thalamus of the same or even larger magnitude. For instance, Sherman and Koch (Sherman and Koch, 1986) estimate that in the cat there are roughly 106 fibers from the lateral geniculate nucleus in the thalamus to the visual cortex, but 107 fibers in the reverse direction.

The corticothalamic projection is made up of two distinct populations, as shown by both their cortical laminar origins and the characteristics of their axonal terminations. Retrograde tracer injections into ventral thalamic nuclei have revealed that corticothalamic neurons from motor cortical regions originate from laminae V and VI (Lund et al., 1975; Jones and Wise, 1977; Nakano et al., 1985; Anderson and DeVito, 1987). Injections of anterograde tracers into motor, somatosensory and auditory cortical areas have shown that the corticothalamic projections terminate with a large population of small, widely distributed spherical endings (Type I) and a smaller population of giant endings found in more restricted regions (Type 2) (Rouiller et al., 1998; Ambardekar et al., 2003).

The relationship between cortical laminar origin and axonal termination was established in cat motor cortex by reconstructing the morphology of single axons labeled with fine focal injections in cat M1 (Kakei et al., 2001). This revealed that the small Type 1 endings are associated with corticothalamic neurons originating in Layer VI, while the axons with giant Type II endings arise from Layer V. The same study showed that the Layer VI projections gave off collaterals to the thalamic reticular nucleus, while the Layer V projections did not. This laminar pattern has also been demonstrated in the S1 and prefrontal cortex of monkey, the cat primary auditory cortex, and the rat S1 and primary visual cortex (Rouiller and Welker, 2000).

Numerous studies have shown that the giant terminals synapse on proximal dendrites (Wilson et al., 1984; Vidnyanszky and Hamori, 1994; Erisir et al., 1997), often within a glomerulus as part of a triad (Bourassa and Deschenes, 1995; Bourassa et al., 1995; Feig and Harting, 1998), while the small terminals contact peripheral dendritic segments of relay neurons.

The substantial morphological differences the between the Layer VI projection with Type 1 endings and the Layer V projections with giant Type 2 endings suggest differences in functional roles as well. The Layer V neurons are glutamatergic and make strong, secure synapses onto ionotropic receptors, often controlling the firing of thalamic relay neurons (Descheenes and Hu, 1990). This projection also shares very similar structural and connectivity characteristics with the retinogeniculate projection, which makes up the driving input to the LGN (Li et al., 2003). It has been directly shown through whole cell recordings in rat somatosensory thalamus and LGN that EPSPs elicited by activation of Layer V corticothalamic neurons were of a large, all-or-nothing nature, similar to those elicited by activation of the retinogeniculate projection. (Reichova and Sherman, 2004). In cases where the function of Layer V neurons was tested, it was shown that they determine the receptive field properties of the thalamic relay neurons (Bender, 1983; Diamond et al., 1992).

Layer VI neurons are also glutamatergic (Baughman and Gilbert, 1980; Fonnum et al., 1981), but in contrast to Layer V CT neurons, they synapse onto both ionotropic

and metabotropic receptors at distal dendrites, making them better suited to produce modulatory effects on thalamic relay neurons(McCormick and von Krosigk, 1992; Godwin et al., 1996). The metabotropic receptor associated with axons of Layer VI neurons produces a slow, long lasting EPSP, and from the distal location of the many small boutons, Layer VI terminations can control the membrane potential of the dendritic tree, but have a more limited effect on the potential at the soma. Functional studies in anesthetized animals show that Layer VI activity can modulate the firing rate (Webb et al., 2002), the spatial and temporal response properties (Funke et al., 1996; Kohn and Worgotter, 1996; Worgotter et al., 2002), and the response mode (burst or tonic) of LGN neurons (Funke and Eysel, 1992).

Much less is known about the activity of corticothalamic neurons and the signals that they actually transmit to the thalamus. The activity of antidromically-identified potential corticothalamic neurons in motor cortex has been studied in the rabbit and cat during postural corrections or locomotion (Beloozerova et al., 2003a; Beloozerova et al., 2003b; Beloozerova et al., 2003c; Sirota et al., 2005; Sirota et al., 2006). These investigators showed that only efferent neurons from layer V were strongly activated during postural corrections or a complex stepping behavior. They also found that the layer VI corticothalamic projection could be further subdivided by conduction velocity into slowly conducting layer VI neurons (~40% of all layer VI CT neurons) and moderately conducting neurons. The slowest conducting layer VI corticothalamic neurons were virtually silent throughout the task, and 39% of the more moderately

conducting layer VI neurons showed low firing rates (~ 1Hz) during step-related behavior.

Stepping and stumbling, as studied in the cat and rabbit, can occur without suprapinal input (Whelan, 1996); therefore, the activity transmitted from the cortex to thalamus via neurons in either layer V or VI could be quite different during a reaching movement. The goal of the present study was to characterize the neural activity of corticothalamic neurons in the awake monkey performing a visually-guided reaching task. We used pairs of stimulation electrodes implanted into VPLo of motor thalamus to identify potential corticothalamic (CT) neurons in MI by antidromic activation and then studied the activity of these potential CT cells during the reaching task.

Methods

Animals

Three juvenile male *Macaca fascicularis* monkeys (monkeys F, J and P) weighing 3.9 – 5.0 kg at the conclusion of these experiments were used. Subjects were obtained by the Washington National Primate Research Center (WaNPRC) at the University of Washington from its breeding colonies administered by Tulane University in Covington, Louisiana. Animals were cared for in accord with the Guiding Principles

in the Care and Use of Animals (National Academy Press, 1996). All procedures were approved by the institutional animal care and use committee of the University of Washington. During the adaptation, training and work periods, animals were maintained on a food restriction protocol, using applesauce (up to 2 cups per day) as a reward to motivate behavior. Water was available in the home cage at all times, and monkey chow and fruit were given on a daily basis. Weights were not allowed to drop below 90% of the original or expected weight.

Apparatus

The animal was perched in a primate chair facing a workspace consisting of three parallel surfaces spaced approximately 6 cm above each other and angled 5° downward towards the monkey (Turner et al., 1995). The top surface was a high-resolution flat-panel computer monitor, with the viewing side facing down, the middle surface was a half mirrored sheet of plexiglass, and the lowest surface was a digitizing pad (Calcomp model # 34120) that made up the working surface for the monkey. The monkey's right arm was free to move across this work surface. The half-mirrored plexiglass in the middle layer was illuminated from below by two 10-watt bulbs placed at the edges of the working surface. In this configuration the animal could simultaneously see his arm on the work surface below the mirror and, in the same plane, the virtual image of the visual stimuli presented on the monitor above.

A plexiglass splint attached to the animal's right arm contained a small, embedded electromagnetic coil (40 kHz, 3mA) that was positioned under the palm. This splint was secured using three straps and extended across the wrist, so as to minimize movement at this joint. When the monkey's palm was positioned flat on the surface of the digitizing pad, the position of the magnetic field produced by the coil in the splint was converted in real time (100 Hz sampling rate) to analog X and Y coordinates with a spatial accuracy of ±0.6 mm. These coordinates were calibrated to match the reflected images of the visual monitor placed above. The sensitivity of the digitizing pad could be controlled by adjusting the current through the coil in the splint. During training periods, this current was adjusted downward, so that the coil had to be located directly on the work surface. In this way the monkey learned to keep his palm flat on the work surface at all times.

The Visual Tempo System (V8.0) (Reflective Computing) was used for behavioral control and data acquisition. Tempo acquired all data at a rate of 1 kHz.

FIG 2.1

Task

All 3 animals were trained to make center out arm movements in response to visual and auditory cues, as illustrated in Fig 2.1. The monkeys were trained to make all movements rapidly by restricting response times to less than 300 ms and movement times to less than 500 ms. Each monkey was first required to hold its hand on a central home target for a variable period (0.6 -1.0 s). At the end of this period one of 8 or 12 psuedo-randomly selected peripheral targets (1 cm diameter), equally spaced and arranged radially around the home position at a distance of 10 cm, was illuminated. After an additional variable hold period (.2 – .4 s), the central home target dimmed and an auditory trigger tone sounded signaling the animal to move its hand to and hold the illuminated target for a variable hold period (0.8 – 1.5 s). Another auditory trigger tone was then delivered, and the animal returned its hand to the home position for a variable time (0.6 – 2.4 s) before an applesauce reward was delivered through a stainless steel spout positioned in front of the mouth. Rewards (~0.5ml) were delivered on a variable schedule, with 40 – 60% of successful trials leading to reward.

Surgical Procedures

After the animal was trained to achieve success rates >90% in the movement task, two chambers were stereotaxically (Szabo and Cowan, 1984) implanted in craniotomies over the left hemisphere, with the use of sterile surgical procedures under

isoflourane anesthesia. A cylindrical chamber (Cilux, 18mm diameter) (Crist, Hagerstown, MD) was angled down 30° posterior to the coronal plane to allow access to anterior nuclei of the dorsal thalamus, with the center of the chamber targeted at VPLo (A9.6, L6, Z7 according to Szabo and Cowen) (Szabo and Cowan, 1984). A second rectangular stainless steel chamber (28 x 15 mm) was angled down 32° anterior to the coronal plane and rotated 28° away from the sagittal plane to allow electrode penetrations normal to the surface of primary motor cortex. The final position of this chamber was optimized during the implant surgery so as to maximize access to the hand and arm-related areas of primary motor cortex. (See figure 2.7 for approximate locations of chambers on monkeys J and P.)

Chambers and nylon tubes placed horizontally to accommodate head stabilization bars were anchored with dental acrylic to a number of stainless steel or titanium screws inserted into the skull.

Neural recording and stimulation

Neuronal recordings were made using sharpened tungsten electrodes (0.005"/0.127mm – 0.01"/0.254mm shaft diameter) that were insulated along the shaft using a polyimide sleeve (Micro-ML Tubing), and along the tapered portion to the tip with several coats of epoxylite resin (Epoxylite Corp., St. Louis)). For recording, the

epoxylite was ground from the tip and the impedance lowered to 70 – 120 kΩ by electrolytic deposition of particulate iron or gold.

Electrodes for recording in thalamus were inserted into the brain through sharpened stainless steel cannulae that penetrated the dura and extended into the brain to a cannula tip position approximately 5 mm dorsal to anterior thalamus. The cannulae and tungsten thalamic recording electrodes were left in place for stimulation in the first monkey, but to reduce the electrode impedance, and therefore the stimulus artifact, stainless steel electrodes (FHC, Inc., Bowdoinham, ME) were used for stimulation in the second and third animals. These electrodes had shaft diameters of 0.01"/0.254mm and were also insulated with polyimide tubing and epoxylite. Final tip exposures were 50-70 μM with impedances of 5 – 40 kΩ. Cortical recordings were performed without the assistance of a dura penetrating cannula. Instead, a blunt cannula was lowered to the surface of the dura, and a sharp 0.008"/0.20mm or 0.01"/0.0254mm shaft electrode penetrated the dura directly.

Two methods were utilized for advancing and positioning the microelectrodes. For acute recording tracks involving one or two electrodes, a hydraulic microdrive (Trent Wells) attached to a custom-built (NPRC Engineering) X-Y positioning stage was directly mounted on the recording chamber on the monkey's head. For chronically implanted stimulating electrodes or recording sessions during which we inserted more than two recording electrodes, we used screw driven microdrives. These were

positioned on a grid with 1 mm center-to-center spacing of gridholes (Crist Instruments) and secured in the recording chamber. Each manipulator held 2 electrodes 2 mm apart and advanced at a rate of 333 microns per full turn of the drive screw. Chronic stimulating electrodes were left in place for up to a month at a time.

Extracellular neural activity was amplified (5 - 32,000X) and filtered (bandpass, 0.25 – 8 KHz) by a Plexon data acquisition system (Plexon, Dallas, TX) and was recorded via a pulse-code modulator (Vetter,model 4000) on videotape (Sony). Action potentials were sorted on-line using dual time-voltage discrimination (Sort Client, Plexon), and when necessary, manual resorting was performed off-line (OFSV2.0, Plexon). Digitized waveforms (40KHz resolution), timestamps and behavioral data were saved on hard disk using the Plexon system.

Placement of thalamic stimulation electrodes

General mapping of the thalamus was first performed by recording neural activity using 0.005" tungsten recording electrodes driven by the hydraulic microdrive. Somatosensory thalamus (VPLc) was easily identified by the brisk, high-frequency, bursty responses to passive and active joint rotation and deep muscle palpitation or light, superficial brushing of hair. Microstimulation in the area located anterior to VPLc, (using the same electrode that was used for recording) elicited movements at a low stimulus threshold (< 100 μA, -/+, 0.2 ms pulse duration, 240 Hz, 12 pulses),

verifying that the electrode was located in the cerebellar receiving nucleus of thalamus (VPLo) (Buford et al., 1996; Vitek et al., 1996). Neurons in this area were also sensitive to joint rotation and/or deep manipulation of muscles. Anterior to VPLo we encountered an area that required higher stimulus amplitudes to elicit movement (up to 500 μA, -/+, 0.2 ms pulse duration, 240 Hz, 12 pulses) and had cells that exhibited no modulation in activity in response to passive movements, both consistent with the characteristics of VA and VLo, the pallidal receiving nuclei of the thalamus. This combination of characteristics allowed reliable identification of thalamic motor nuclei using recording and stimulation techniques.

After identification of regions of arm-related motor thalamus, pairs of tungsten (monkey F) or stainless steel (monkeys J and P) electrodes (0.01"/0.254mm), with impedances of 5 - 40 kΩ, were lowered into VPLo or VLo using the screw-driven, grid-mounted microdrives. Electrode pairs were positioned so that the tips were located within, or bracketing, an area containing cells that showed arm-related or task-related activity, based on previous thalamic mapping tracks. The electrodes were spaced 2mm apart and were lowered until single or multiunit activity was observed that changed with movement of the arm during the task. Placement of thalamic stimulation electrode pairs and results from stimulation in Monkey P are shown in Figure 2.2.

FIG 2.2

Data acquisition

We used microstimulation (up to 50μA, 12 biphasic pulses, 240 Hz) and sensorimotor mapping to identify task-related arm areas of M1. Electrode penetrations were then made throughout these arm-related cortical areas while we searched for neurons that were activated antidromically by the thalamic stimulating electrodes.

During search periods the stimulation paradigm for identification of antidromically activated neurons consisted of a single cathodal/anodal, biphasic stimulation pulse applied between two thalamic stimulating microelectrodes separated by 2mm, with a pulse duration of 0.2 ms per phase and amplitudes ranging from 500 uA to 1 mA. Interspersed among the single search pulses were short trains of 3-12 pulses delivered at 120 or 240 Hz designed to elicit orthodromic responses or local field potentials in the cortex.

When a well-isolated cortical cell responded to a search pulse we conducted additional tests to distinguish antidromic from orthodromic activation. Neurons exhibiting 1) responses with constant latencies to stimulation (<0.2 ms jitter), 2)

responses that reliably followed a high-frequency stimulus train (3-6 pulses at 120 Hz), and when possible, 3) a positive collision test when stimulation was triggered by a spontaneous action potential, were considered corticothalamic neurons with antidromic responses to thalamic stimulation (Finlay et al., 1976; Fuller and Schlag, 1976). For antidromically activated neurons, threshold currents (50% probability of activation) were determined, and for latency and collision tests we stimulated with 140% of threshold current. The latency of an orthodromic or antidromic response to stimulation was measured as the time from stimulation delivery (onset of stimulation artifact) to the beginning of the evoked action potential. Neurons were classified as orthodromically activated if they failed the tests for antidromic activation but still responded to >50% of stimulus presentations with at least one spike (Swadlow, 1994). Neurons exhibiting a decrease in activity following stimulus delivery for any 2 consecutive 10ms bins, when compared to the 100ms period prior to stimulation (ANOVA, $p<0.05$), were classified as orthodromically inhibited. Examples of identified antidromic responses are shown in Figures 2.3 and 2.4, and examples of orthodromic activation are shown in Figure 2.6.

FIGS 2.3 and 2.4

Data analysis

Customized Matlab code (Mathworks) was used to calculate instantaneous tangential velocity from X and Y hand positions by differentiation. The times of movement initiation (M), peak tangential velocity (P), and end of movement (E), were determined automatically using threshold and duration criteria for the tangential velocity signal. We used visual inspection to confirm the accuracy of these behaviorally defined events, and we made adjustments when necessary.

Baseline firing rates were defined as the averaged mean firing rate during a 500 ms control period beginning 200 ms after the start of the trial (hold home; see Fig 2.1). Other epochs used in the analysis of neural data were the perimovement period (300 ms centered on peak velocity (P)), and the reward period (300 ms beginning with the delivery of reward). We compared the average neural activity during each of these periods with the baseline firing rate obtained during the control period. An epoch was considered to have a task-related change in neural activity if its average firing frequency differed significantly from baseline discharge rate (ANOVA, $P<0.01$), with the onset of the change defined as occurring at the beginning of the first of 3 consecutive 10ms bins with discharge rates differing from the baseline rate (ANOVA, $P<0.01$).

Directional specificity of a neuron's discharge was determined using the perimovement mean firing rate of a CT neuron for arm reaches to each target direction.

Cells that showed a significant effect of the direction of movement on cell discharge rate (ANOVA, $P<0.05$) were considered to have directional specificity. The directional tuning characteristics of these CT neurons will be discussed in greater detail in Chapter 3.

Results

A total of 126 antidromically-activated (presumed) corticothalamic (CT) neurons were identified in the arm region of primary motor cortex in three monkeys (22 in F, 36 in J and 68 in P). An additional 312 cortical neurons were activated orthodromically. No neurons showed both antidromic and orthodromic responses to thalamic stimulation. Neurons were selected for inclusion in this study if they showed a response to thalamic stimulation; they were not prescreened for task-related activity.

Thalamic stimulation identified two classes of antidromically activated neurons with different spontaneous activity

Thalamic stimulation produced antidromically evoked spikes in 126 neurons located throughout the arm region of the primary motor cortex. Examples of antidromic

identification of 2 neurons at short and long latencies are shown in Figures 2.3 and 2.4. The short latency neuron (Fig 2.3) had spontaneous activity in the absence of thalamic stimulation, and spikes evoked by thalamic stimulation showed occlusion (collision) with a spontaneously occurring spike (Fig 2.3B). The spike evoked by thalamic stimulation had a constant latency of 3.4ms at threshold (Fig 2.3C), and followed each stimulus pulse delivered at 125 Hz (Fig 2.3D).

The long-latency neuron (Figure 2.4) showed no spontaneous activity, but was reliably activated at a constant latency (22.3ms) with stimulus intensities above threshold (Fig. 2.4A and 2.4B) and consistently followed a stimulus train of 20 Hz (Fig 2.4C). Slowly conducting axons are likely to show impulse failure during a high frequency tetanus, so not all neurons were tested at high stimulus rates(Swadlow, 1985, 1998). Because this cell had no spontaneous or synaptically evoked activity, a collision test could not be performed.

In the absence of thalamic stimulation, antidromically activated cortical neurons were classified by their level of spontaneous activity. Eighty-one of the 126 corticothalamic neurons had activity while the hand was held still and/or in association with movement. These were referred to as "active" CT cells.

The remaining 45 corticothalamic neurons had no spontaneous activity in association with the task or with arm movements. Their presence was only detected by

the fact that they responded antidromically to thalamic stimulation. These were referred to as "inactive" CT neurons. Two of these cells did show very low rates of discharge during the recording session (< 1 spike/minute). However, neither showed any modulation with the task or with movement.

We tested several of the inactive neurons outside of the normal recording session in an attempt to identify stimuli that would produce neural activity. We presented novel targets (differing in size, shape, color, location or timing) or images (pictures of monkeys or predators) during the task, performed extensive sensorimotor examinations, allowed the monkey to engage in spontaneous behavior, and let the monkey fall asleep and then awoke it in an attempt to elicit neural activity. However, none of these conditions caused the inactive neurons to produce action potentials.

Figure 2.5

Depth of activated cells and antidromic threshold and latency and are "correlated" with spontaneous activity

The depth at which active and inactive CT neurons were located was significantly different (ANOVA, $p<0.001$). The active neurons were found more

superficially (Fig 2.5C and 2.5D, red, mean depth = 1615 μm) than the inactive neurons (Fig 2.5C and 2.5D, blue, mean depth = 1792 μm). The active neurons were also distributed over a larger range (727 μm) than the inactive cells (209 μm). A more detailed discussion concerning the depth of cortical responses follows in a separate section.

As shown in Figures 2.5A-C, the threshold stimulus current necessary to evoke action potentials antidromically from the thalamus ranged from 20 to >1000 μA. Although there was some overlap, cells with low antidromic thresholds (less than 500 μA) most often had spontaneous activity (red, mean threshold = 285 μA), whereas those with no spontaneous activity (blue, mean threshold = 627 μA) usually had higher antidromic thresholds (ANOVA, $p<0.001$).

Antidromic latencies ranged from 1.3 to 24 ms, and again, the distribution was different for active and inactive cells (ANOVA, $p<0.001$), as shown in Figures 2.5A and D. All but 2 of the active cells had antidromic latencies less than 10 ms (Fig 2.5D, red, mean latency = 3.43 ms), with most less than 4 ms, whereas most (40/45) of the inactive cells had latencies greater than 8 ms (Fig. 2.5D, blue, mean latency = 12.1 ms).

Because the threshold was so high for antidromic activation of some neurons, it was possible that the axons activated did not terminate in the thalamus, but were located in the internal capsule and activated by current spread. This is unlikely because the

majority of our stimulation sites were far (>4mm) from the internal capsule (see Figure 2.2), and current spread over this distance is not in accord with previous studies, which show that effective current spread is limited to a sphere <2 mm in diameter around a stimulation site with stimulation of 1mA (Stoney et al., 1968). Moreover, for stimulation sites closer to the internal capsule we tested for the possibility of activation by current spread to capsular fibers by advancing and withdrawing the stimulation electrodes along their tracks while recording from a single CT neuron. Stimulation produced antidromic effects from a very restricted region, and, as the stimulation electrodes moved away from their starting position, stimulation failed to produce antidromic responses, even when the electrodes were advanced towards the internal capsule. This shows it is unlikely that current spread was activating axons in the internal capsule.

The stimulation strategy employed with Monkey F was different from that used in Monkeys J and P, and this largely explains the lack of active corticothalamic neurons found in Monkey F. In this monkey, the tungsten stimulation electrodes were electroplated with gold to increase surface area and reduce the electrode impedance. However, after an extended period of stimulation, breakdown occurred at the tip of the electrodes, causing an increase in impedance and creating a saturating stimulation artifact with a duration of up to 4ms (Fig 2.4B). These conditions are likely to have obscured many responses that in other animals had latencies shorter than 5ms. In Monkeys J and P, the artifact was greatly reduced and the electrode impedance lowered

by using stainless steel electrodes with large exposures at the tip (70 μm). The artifacts with these electrodes were much smaller, as seen in Figure 2.3, which revealed antidromic spikes at short latencies.

FIG. 2.6

Orthodromically evoked cortical responses

Thalamic stimulation also produced variable latency orthodromic responses in cortex (n=312), as seen in Figure 2.6. A single thalamic stimulation pulse was often sufficient to elicit a response in the cortex across a wide range of latencies (Fig 2.6A and B). These responses were distinguished from antidromic responses by the absence of a consistent latency at threshold stimulus intensity and by the large variance in response latencies to stimulation. Some orthodromic responses required multiple stimulation pulses, such as that shown in Fig 2.6C, which required a train of three stimuli. In approximately 14% (43/312) of the cells with orthodromic responses, thalamic stimulation produced an inhibition of ongoing cortical activity (Fig 2.6D).

Cortical extent of responses to thalamic stimulation

We estimated the breadth of dispersion of corticothalamic axons and thalamocortical axons by determining the extent over which cortical neurons were activated antidromically or orthodromically by thalamic stimulation.

A total of 151 cortical penetrations were made with thalamic stimulation electrodes in place (87 in J and 64 in P) in the two monkeys with stainless steel stimulation electrodes (Figure 2.7). Orthodromic responses were observed in 114 penetrations, antidromic responses were found in 52, and both types of response were found in 39, although no cells were activated both antidromically and orthodromically. Twenty-four penetrations contained cells that exhibited no response to stimulation.

Figure 2.7

The antidromic responses obtained from single thalamic stimulation pairs were located in small focused regions (mean cortical surface area = 5.5 mm^2, 5 penetrations) that we called antidromic response fields. The corresponding area that contained all the orthodromic responses from the same pair of stimulation electrodes, the orthodromic

response field, was larger (mean area 14mm^2, 11 penetrations) and usually encompassed the entire antidromic response field.

Figure 2.8

Figure 2.8A shows the locations of all cortical penetrations made with a single pair of thalamic stimulation electrodes (pair represented by green squares in Fig 2.2) and the identified orthodromic and antidromic response fields. Of the 19 cortical penetrations made with this thalamic stimulation pair, antidromic responses were obtained in 5, with an antidromic response field of 4.5mm^2, and orthodromic responses were obtained in 12, forming an orthodromic response field of at least 13mm^2. Orthodromic and antidromic responses were found in three penetrations, but the different response types were never found in the same cell. Five penetrations, marked by an X, showed no response to thalamic stimulation and helped define the outer border of the orthodromic response field.

We obtained detailed maps, similar to that shown in Figure 2.8, of orthodromic and antidromic response fields using 5 thalamic stimulation pairs (3 in monkey J and 2 in monkey P). Cortical orthodromic response fields associated with different thalamic stimulation pairs occasionally overlapped (data not shown). However, cortical

antidromic response fields associated with different stimulation pairs did not show overlap, except when the areas stimulated in thalamus also overlapped, suggesting that divergence in the CT projection is limited (although each stimulation pair encompassed a 2 mm separation distance).

Depth of cortical responses to thalamic stimulation

A representative example of track reconstructions indicating the depths at which orthodromic and antidromic responses were found is shown in Figure 2.8B. The five electrode penetrations along the red line in Figure 2.8A are replotted in 2.8B showing the depths at which different types of activity were encountered along each individual penetration. As discussed in the previous section, antidromic response fields were small, in this case including only the middle three penetrations. The larger orthodromic response field includes all 5 penetrations.

Orthodromic responses (circles) were encountered at an average starting depth of 650 microns below the onset of neural activity (the triangles in Fig 2.8B), while antidromic responses (squares) appeared at an average depth of 1350 microns. Orthodromic responses were encountered over a longer range (mean = 900 μm) than the antidromic responses (mean = 450 μm).

Of the 39 penetrations with both orthodromic and antidromic responses, the initial (most superficial) response to thalamic stimulation was always orthodromic. In 4 penetrations the orthodromic range overlapped with the antidromic range, but in each of these cases, only a single antidromic response was identified within the orthodromic range (Fig 2.8B, 2nd track). Also, in the 39 penetrations with both response types, the antidromic range always extended deeper than the orthodromic range.

Spontaneous and task-related activity of active CT neurons

The 81 active CT neurons showed varying degrees of spontaneous activity and modulation with different aspects of the task. These neurons discharged at mean rates of 3.6 to 65.0 Hz (overall mean = 14.6 ± 7.3 Hz) with the hand stationary on the hold home position, 2 to 141.7 Hz (overall mean 34.8 ± 16.1 Hz) during the perimovement period, and 3.4 to 72.2 Hz (overall mean 21.3 ± 12.7Hz) during the hold target period. Various examples of task-related modulation of the spontaneously active neurons are shown in Figure 2.9.

Figure 2.9

Perimovement relationships

Seventy-nine CT neurons showed perimovement modulations when compared with baseline firing rates during the control period. Seventy-three (92%) of these exhibited significant directional tuning during this period. Figure 2.10 shows an example of data from a neuron with strong directional activation during movements towards targets in the upper left region of the workspace (away from and to the left of the monkey). Movements to targets in the lower right areas of the workspace caused little or no change in the activity of this neuron. The majority (63) of CT neurons with perimovement modulations showed only increases in activity during trials in all directions, while the remaining 16 neurons showed more complex combinations of increases and decreases in activity associated with arm movement in different directions. The directional tuning characteristics of these CT neurons will be discussed in greater detail in Chapter 3.

Discussion

The current results show that the corticothalamic projection from primary motor cortex to motor thalamus (VPLo) in *M. fascicularis* can be functionally separated into two populations. One group of CT neurons remains virtually silent during a visually

guided arm reaching task performed by a well-trained monkey. In addition to the lack of spontaneous activity during the task, these neurons were also silent during all other tested periods. They were only detectable by the presence of action potentials elicited antidromically by stimulation in the thalamus. The second group of corticothalamic neurons exhibited task-related activity that is similar to that typically reported in M1. (Evarts, 1968; Georgopoulos et al., 1982; Evarts et al., 1983; Schwartz and Moran, 2000; Scott, 2003; Hatsopoulos, 2005). The activity of these spontaneously active neurons was modulated during the perimovement periods, and the amplitudes of the task-related modulations during reaching in different directions were broadly tuned to a circular normal distribution.

Two classes of corticothalamic neurons

Our findings are consistent with the known dual morphological characteristics of the corticothalamic projection in the motor system, with large corticothalamic neurons projecting from cortical Layer V directly to large boutons on proximal dendrites in the thalamus, and smaller, but much more numerous CT neurons projecting from cortical Layer VI and terminating with small boutons on distal dendrites in the thalamus. We propose that the silent neurons we recorded from correspond to the Layer VI population of CT neurons, while the spontaneously active neurons are part of the Layer V projection.

Our stimulation data also support this proposal. The silent neurons had long antidromic latencies and high thresholds to stimulation and were found at deep locations in our recording tracks, consistent with them being the CT neurons with small, unmyelinated axons found in Layer VI . Spontaneously active neurons had shorter latencies, lower thresholds to stimulation and were found more superficially within a recording track, consistent with the characteristics of neurons with large myelinated axons that originate in Layer V.

Other studies have also shown that slowly-conducting CT neurons in layer VI of the primary motor cortex are silent or have very low spontaneous firing rates during locomotion and postural corrections in awake rabbits or cats (Swadlow, 1994; Beloozerova et al., 2003a; Beloozerova et al., 2003b; Sirota et al., 2005). A small percentage of these layer VI CT neurons did have an extremely low rate of discharge during rest or locomotion, but most were only evident because they responded to thalamic stimulation. The few neurons that did show task-related activity linked to particular phases of the step cycle in cat were part of the moderately conducting population of layer VI neurons. This group of neurons has not been described before and may represent a different population from more commonly reported slowly conducting layer VI corticothalamic neurons.

Based on the evidence for the layer VI corticothalamic projection's involvement in the modulation of thalamic relay neuron activity, there are numerous circumstances under which one might expect the layer VI projection to be active. The ability of cortical feedback to contribute to receptive field tuning in the LGN and possibly affect the saliency of stimuli via focal changes in the contrast/response gain suggests that the layer VI projection in the visual system might actively influence visual attention (Sillito et al., 1994; Funke and Worgotter, 1997; Suder and Worgotter, 2000).

Other experiments were performed to investigate the role of cortical feedback in the generation of specific brain states as reflected in the structure of the EEG, with specific proposals that the corticothalamic projection is involved in the generation and synchronization of fast and slow oscillations in thalamocortical networks, particularly those associated with sleep states (Murphy and Sillito, 1996; Steriade et al., 2001). The divergent component of the layer VI corticothalamic projection is also well suited to support long range thalamocortical synchronization of thalamically generated rhythms such as sleep spindles and δ waves (Contreras et al., 1996; Contreras and Steriade, 1997). Despite the proposals that layer VI corticothalamic neurons might be active in conjunction with shifts of attention or arousal state as proposed in these studies, we did not observe any such activity.

The active population of CT neurons, possibly corresponding to the Layer V CT projection, was indistinguishable from most other M1 cortical recordings that were not

activated antidromically from the thalamus. (Ruffo, in preparation). There has been a series of studies in which layer V corticothalamic neurons were identified by antidromic activation in the M1, S1, S2, and V1 cortical areas in awake rabbit preparations (Swadlow, 1988, 1989, 1990, 1991, 1994; Swadlow and Hicks, 1996; Swadlow, 2000). These studies focused on characterizing axonal properties, receptive fields and subthreshold inputs with little emphasis on neural activity associated with behavior. However, they did show that layer V corticothalamic neurons have spontaneous activity in all areas of cortex studied. Additionally, in the same studies cited above in which Layer VI corticothalamic neurons were found to be virtually silent, antidromically identified layer V corticothalamic neurons were found to have moderate to high rates of strongly task-related activity (Swadlow, 1994; Beloozerova et al., 2003a; Beloozerova et al., 2003b; Sirota et al., 2005). These results are comparable with our findings, with the possible exception that their stepping and postural tasks might not require strong cortical control (Whelan, 1996).

Drivers vs modulators of thalamic activity

Sherman and Guillery (Sherman and Guillery, 1998) suggest that corticothalamic cells from Layer V should be classified as drivers and those from Layer VI, as modulators. In their terminology, drivers are the source of the essential pattern of

activity in the thalamic neurons, whereas modulators control the effectiveness of drivers.

In primary sensory thalamic nuclei, such as the LGN or VPLc, drivers are predominantly sensory inputs from the periphery that terminate with large boutons near the soma. The cortical input to these sensory nuclei is primarily from layer VI, which would be expected to exert a modulatory action, based on the size and distribution of terminals located in opposition to metabotropic receptors.

Thalamic nuclei outside of the primary sensory ones, including the "motor nuclei", receive corticothalamic input from both layers V and VI, proposed as drivers and modulators, respectively. Due to the presence of a cortical driving input, these thalamic nuclei are considered 'higher-order' and are proposed to have a role in corticocortical communication (Guillery, 1995). Furthermore, Guillery suggests that since the Layer V corticothalamic projections from cortex are branches of axons going to motor or premotor centers in the brainstem or spinal cord, the corticocortical communication is designed to send a copy of current motor information, an efference copy, throughout cortical areas primarily involved in perception (Guillery, 2003).

The thalamic nuclei that make up the motor thalamus receive their major subcortical inputs from the basal ganglia and the deep cerebellar nuclei and receive both large, potentially driving and slow, potentially modulatory corticothalamic inputs

(Rouiller et al., 1998). The basal ganglia receiving regions (VLo and VA) receive tonic high-frequency inhibitory inputs from the internal globus pallidus (GPi) and the reticular portion of the substantia nigra (SNr) (Snodderly et al., 1978), while the cerebellar receiving nuclei (VPLo, VLc, and Area X) receive tonic high-frequency excitatory inputs from the deep cerebellar nuclei (Uno et al., 1970). There is little or no overlap between basal ganglia-receiving and cerebellar-receiving populations of thalamic neurons (Ueki et al., 1977).

The cerebellar afferents make secure synaptic contacts with a high probability of driving the postsynaptic thalamic neurons (Uno et al., 1970; Shinoda et al., 1985; Holdefer et al., 2000; Sakai et al., 2002). Thus, in cerebellar-receiving areas of the thalamus, including the VPLo target of M1, driving inputs could come from both the cerebellar nuclei and the cerebral cortex.

Basal ganglia-receiving areas of the motor thalamus (VLo and VA), however, receive a high-frequency inhibitory, not excitatory, input from the internal segment of the globus pallidus or the reticular portion of the substantia nigra. If this were to act as a "driver", it would have to be an "inverse driver", exciting thalamic neurons, for example, by disinhibition. In fact, Person and Perkel (Person and Perkel, 2005) have found that large calyx-like GABAergic terminals of afferents to thalamus from pallidal-like neurons in the zebrafinch can produce post-inhibitory rebound spikes that have phasic patterns typical of those elicited by the bird's own song.

It is also possible that layer V CT neurons provide the input that primarily shapes the activity of thalamic cells that receive inhibitory input from the basal ganglia. This would be consistent with the finding that injections of muscimol into GPi that produced interruption of pallidal output sufficient to produce increases in tonic thalamic rate did not completely abolish the phasic movement-related discharge of the same thalamic neurons (Inase et al., 1996).

The function of CT neurons projecting to the thalamus

There has been considerable speculation about the function(s) of CT neurons, especially those in layer VI. Some of this has been driven by slice studies in the visual and somatosensory system, in which there was spontaneous activity inlLayer VI CT neurons (Swadlow, 1989, 1990; Sillito et al., 1993; Worgotter et al., 1998). Stimulating the layer VI CT projection in slices produced numerous significant results. In some studies, stimulation changed the tonic discharge properties of thalamic relay neurons, driving a cell from burst to a tonic mode (Funke and Eysel, 1992). Others suggested that activity in the layer VI projection strongly influenced oscillatory activity throughout a corticothalamic loop (Contreras et al., 1996; Murphy and Sillito, 1996; Steriade, 2001). Yet other *in vivo* studies showed a link between arousal or wake states (Steriade et al., 2001).

The contribution of layer VI CT neurons in awake animals remains a mystery, since they had no activity in our task or during a variety of stimulus presentations in and out of the instrumented behavior booth, manipulation of the limbs, and sleep/wake transitions. Nor have others found activity during locomotion, including locomotion over obstacles, a task that the authors believe requires the cerebral cortex and is also visually targeted (Swadlow, 1994; Beloozerova et al., 2003a; Beloozerova et al., 2003b; Sirota et al., 2005).

Because deep layers of cortical cells cannot yet be inactivated exclusively, selective lesions of layer VI neurons have not been able to reveal an action in awake animals. Some nonspecific lesion/inactivation studies indicate that CT fibers whose layer of origin cannot be determined may contribute significantly to the phasic task-related signals in neurons of the thalamus (Kalil and Chase, 1970; Worgotter et al., 2002; Eyding et al., 2003). The most elegant of these (Worgotter et al., 2002; Eyding et al., 2003) have used retrograde transport from the thalamus of a compound that can induce apoptosis of corticothalamic neurons. This compound, chlorin E_6, is conjugated to transported latex nanospheres and, after sufficient transport time, laser illumination of the cortex with long wavelength light induces the release of singlet oxygen that induces targeted apoptosis of CT neurons without damaging other cortical cells (Worgotter et al., 2002; Eyding et al., 2003). However, it cannot selectively destroy a particular subset of CT neurons, such as layer V or layer VI.

This destruction of corticothalamic neurons, done in the visual cortex with nanospheres injected into LGN, (Eyding et al., 2003) abolished the normal dependence of cortical cells on EEG state. Normally, visual responses in LGN are more tonic during the desynchronized EEG state, whereas they are shorter and more phasic when the EEG is synchronized, as in sleep (Baker and Malpeli, 1977; Funke and Eysel, 1992; Worgotter et al., 1998). Such an effect on the activity of thalamic neurons during sleep vs. waking is consistent with layer VI CT actions proposed by Steriade and Sherman.

Summary

In summary, we identified two functionally distinct groups of corticothalamic neurons: a population that was virtually silent during an arm reaching task and a second population that exhibited task-related activity. We propose that the silent population arises from cortical Layer VI and that its function remains undetermined. A possible role for these neurons is to exert a modulatory effect on thalamic relay neurons, but we cannot identify the behavior under which such a modulatory effect is active. Although several other studies support this idea, particularly in the visual system, none have shown a modulatory effect in the motor system of an awake performing animal. We presume that the population with robust task-related activity is the Layer V corticothalamic projection and is a collateral of the corticofugal projection from motor cortex. Our study supports the hypothesis that the motor thalamus is receiving an

efferent copy of the motor output of the cortex, as put forth by Guillery and Sherman (Guillery and Sherman, 2002). However, the evidence presented here does not directly address how the corticothalamic projection affects the activity of neurons in the thalamus. We will address this issue in a future paper (Chapter III).

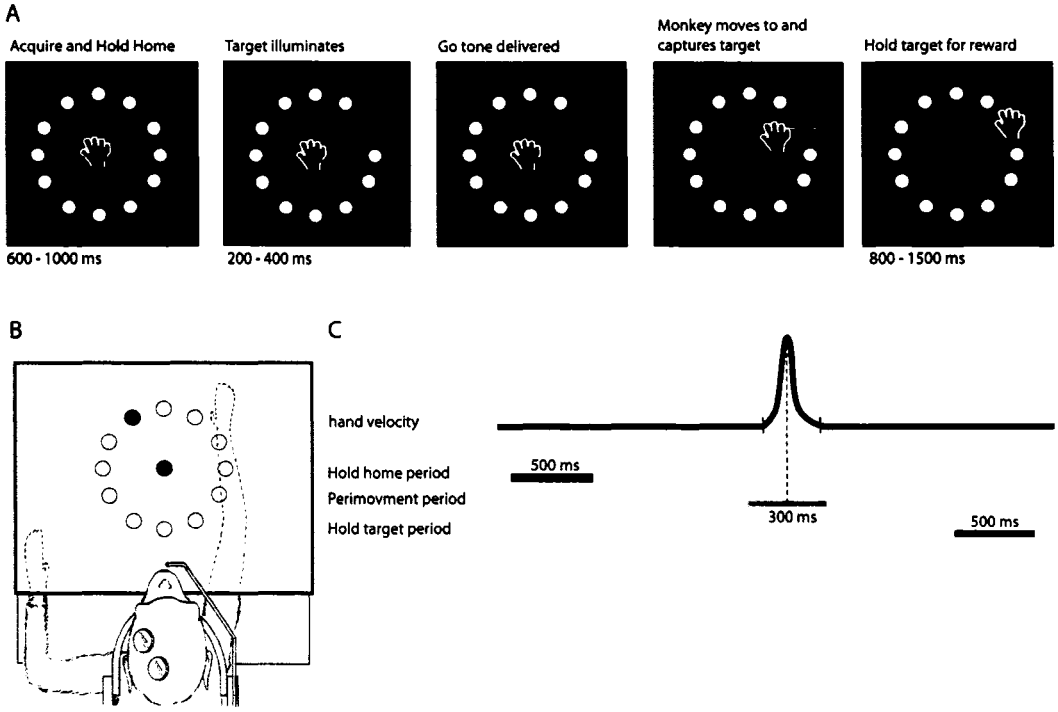

Figure 2.1. Schematic of the task and workspace. **A**, The row of diagrams represents the stages and events during a single trial of the task. The timing associated with each stage of the trial is represented below each diagram. **B**, A top down view of the monkey and the workspace. The monkey's arm, shown by the dotted lines, is below a half-mirrored panel, onto which the targets are presented. The subject can see its arm and the projected images. **C**, A temporal representation of the epochs during a trial and the typical behavior of the monkey. The hand velocity is represented by the dark line, with the hold home, perimovement and hold target periods shown by the colored bars aligned below.

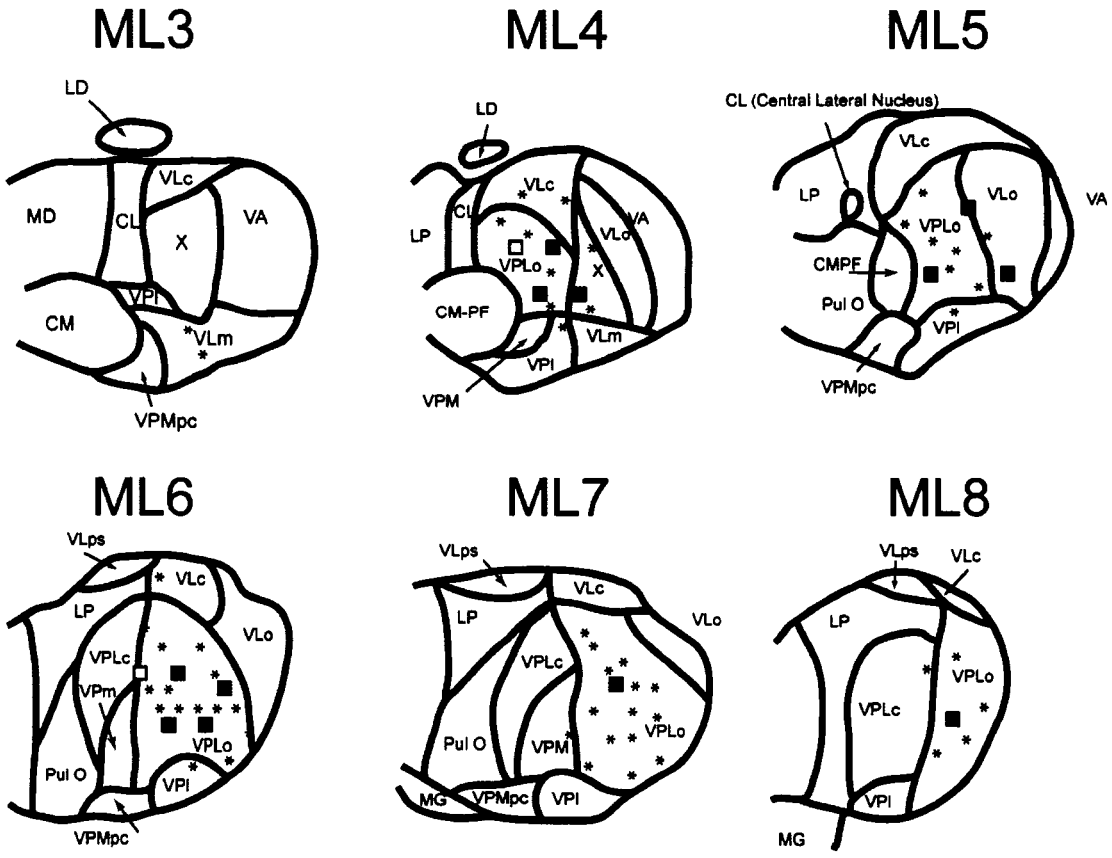

Figure 2.2. Schematic of parasagittal sections through the thalamus indicating the placement of thalamic stimulating electrode pairs and microstimulation effects in monkey P. Colored squares represent the approximate locations of stimulation electrode tips. Stars show locations where microstimulation (240 Hz, biphasic, <50μA) elicited arm movements at low thresholds.

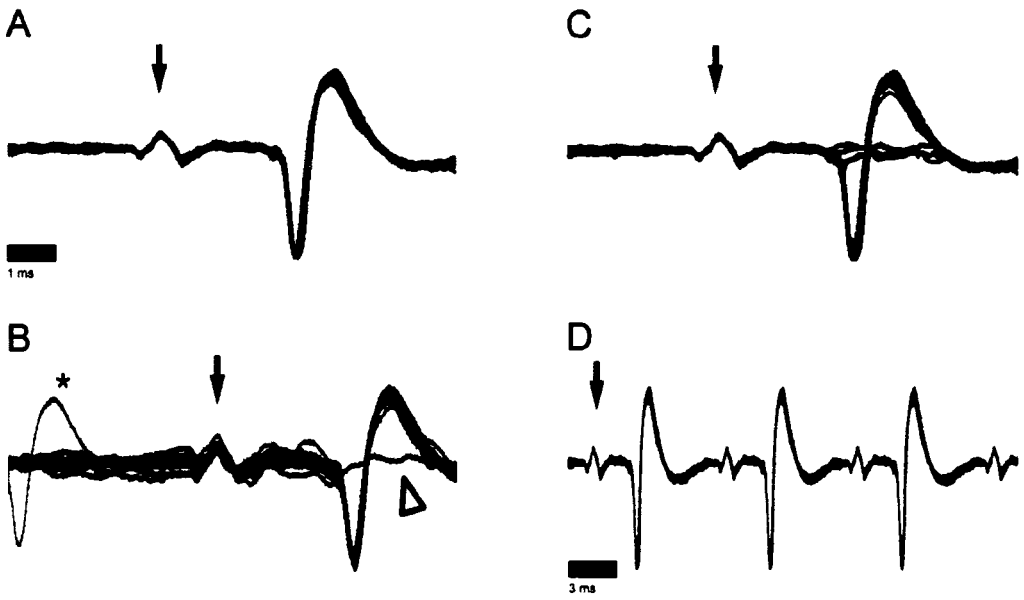

Figure 2.3. Examples of antidromically driven action potentials, recorded in M1. Stimulation electrode was located in motor thalamus (VPLo). **A**, Superimposed records of successive trials demonstrating constant latency response (3.4 ms) to each biphasic stimulation (200ms duration each phase, 90μA). The arrow (⬇) points to the stimulation artifact. **B**, When spontaneous spiking occurred shortly before the stimulation was delivered, the antidromically elicited spike was absent from the recording. This is taken as evidence for a positive collision test. The open triangle (△) indicates lack of an action potential after the spontaneous spike. **C**, Stimulation at 60μA produced action potentials approximately 50% of the time. **D**, The antidromic action potential was able to consistently follow stimuli in a train of 125 Hz.

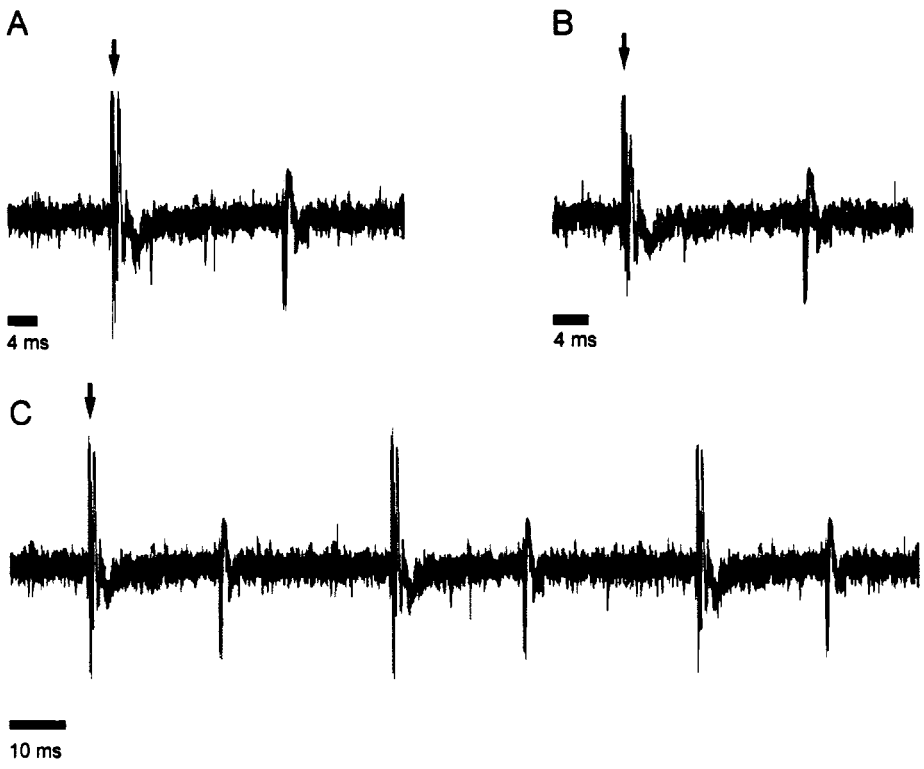

Figure 2.4. Recordings from a "quiet" antidromically driven cortical neuron. Stimulation pair was located in VPLo. **A**, Constant latency response (22.3 ms) to biphasic stimulation (200ms each phase, 700 μA) arrow points to stimulation artifact. **B**, Stimulation at threshold (570 μA) produced action potentials 50% of the time. **C**, An antidromic action potential consistently followed a stimulus train of 20 Hz.

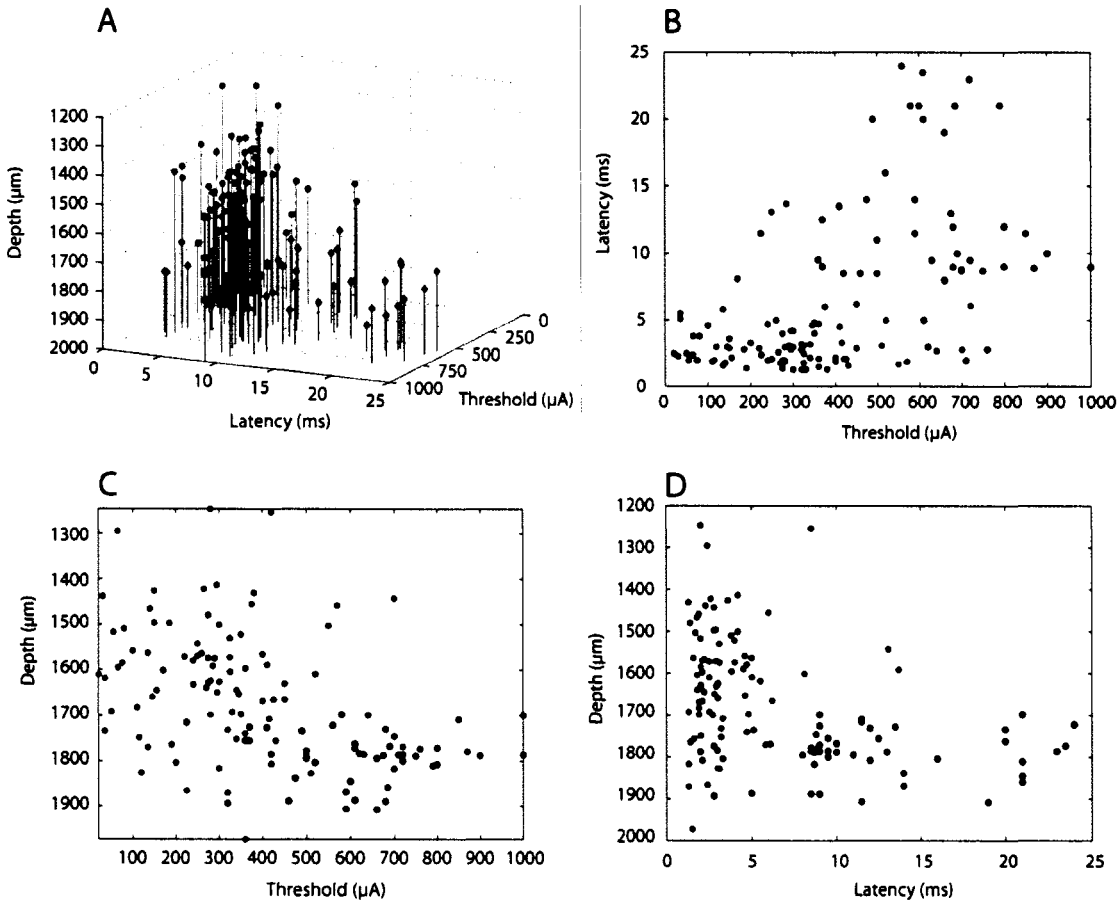

Figure 2.5. Latency, threshold and depth characteristics of antidromically activated cortical neurons. Red circles represent neurons that showed spontaneous activity and blue circles represent neurons with no spontaneous activity. All four projections of these characteristics show clear separations based on the presence or absence of spontaneous activity. **A**, Three axis stem plot of latency vs. depth vs. stimulation threshold. **B**, Scatter plot of threshold vs. latency. **C**, Scatter plot of threshold vs depth. **D**, Scatterplot of latency vs. depth.

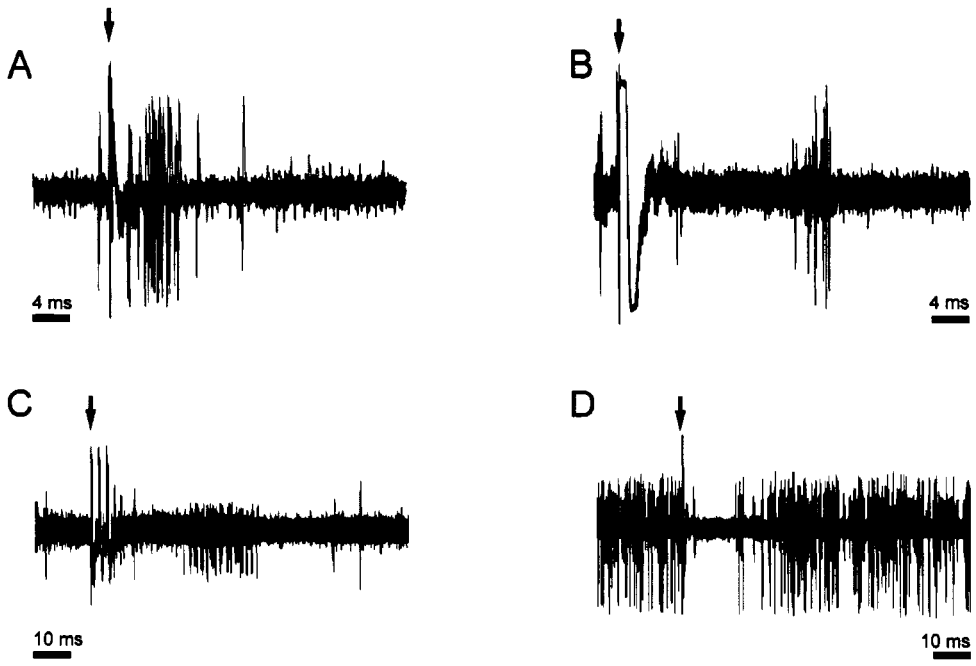

Figure 2.6. Examples of orthodromic responses to thalamic stimulation. Each example shows multiple overlaid stimulation trials. **A**, Short latency (~6.4ms) orthodromic responses to a single thalamic stimulation pulse (300 μA). **B**, Longer latency (~18.5ms) orthodromic responses to a single stimulation pulse (800μA) **C**, Long-latency response (~44ms) that required a train of thalamic stimulation pulses (3 pulses, 400μA) **D**, A single thalamic stimulation pulse (800 μA) led to an inhibition of cortical activity for a period of ~ 20ms.

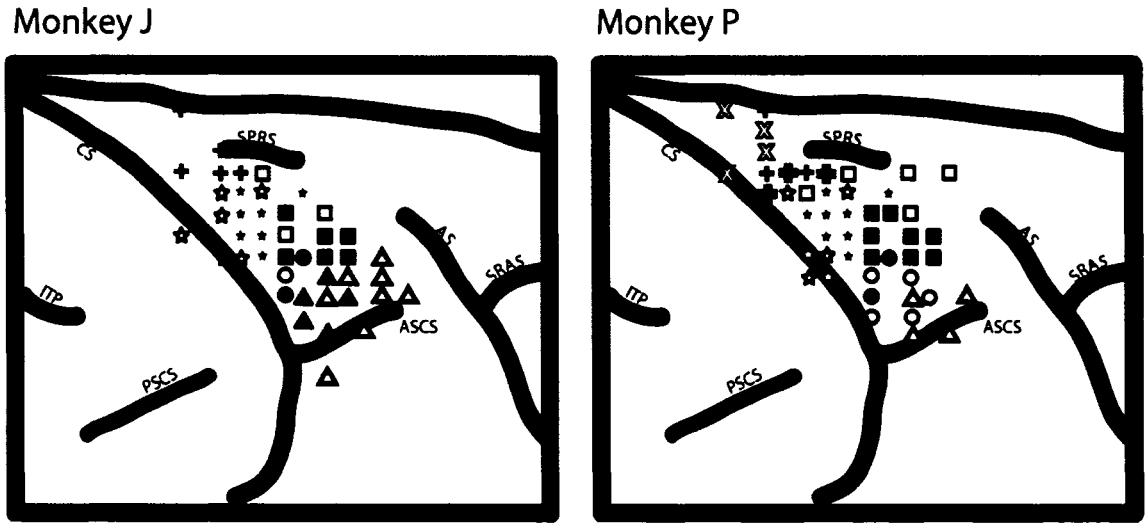

Figure 2.7. Locations of recording tracks in the motor cortex of monkeys J and P. Shapes indicate the location of movement elicited by microstimulation (<50 μA). Filled shapes indicate that antidromically driven cells were recorded in that location. ✙ - trunk, ☆ - shoulder, □ - elbow, O - biceps, △ - hand, CS - central sulcus, SPRS - superior precentral sulcus, ASCS - anterior subcentral sulcus, AS - arcuate sulcus, PSCS - posterior subcentral sulcus, ITPS - intraparietal sulcus, SRAS - superior ramus of the arcuate sulcus)

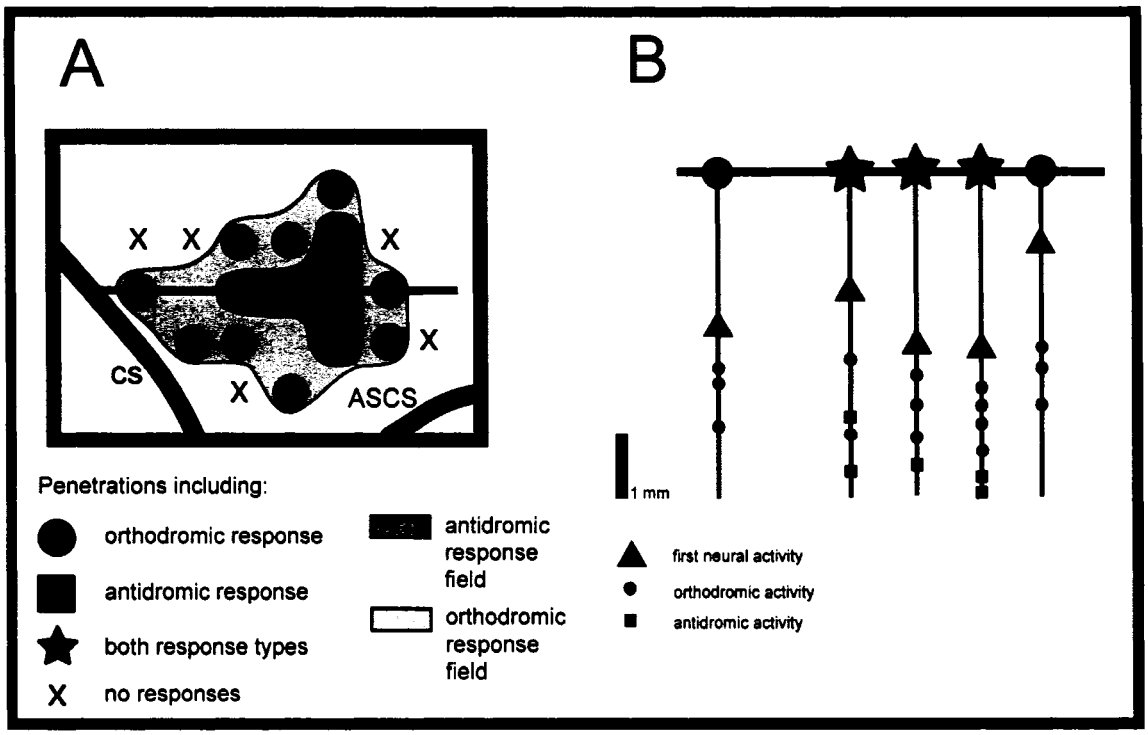

Figure 2.8. Spatial relationships of orthodromic and antidromic responses in Monkey P. **A**, Locations of cortical recording tracks with stimulation effects. These tracks were all run with the same thalamic stimulation electrode pair in place (represented by the green squares in Fig 2.2). Note that the orthodromic effect is present over a wider area than the relatively constrained antidromic effect. **B** - The recording tracks along the red line in A are represented here showing the depths of responses. The red line also represents the point of contact with the dura by the recording electrode. Orthodromic responses were always seen more superficially in the track in this sample. Orthodromic responses were also rarely seen very deep in the track.

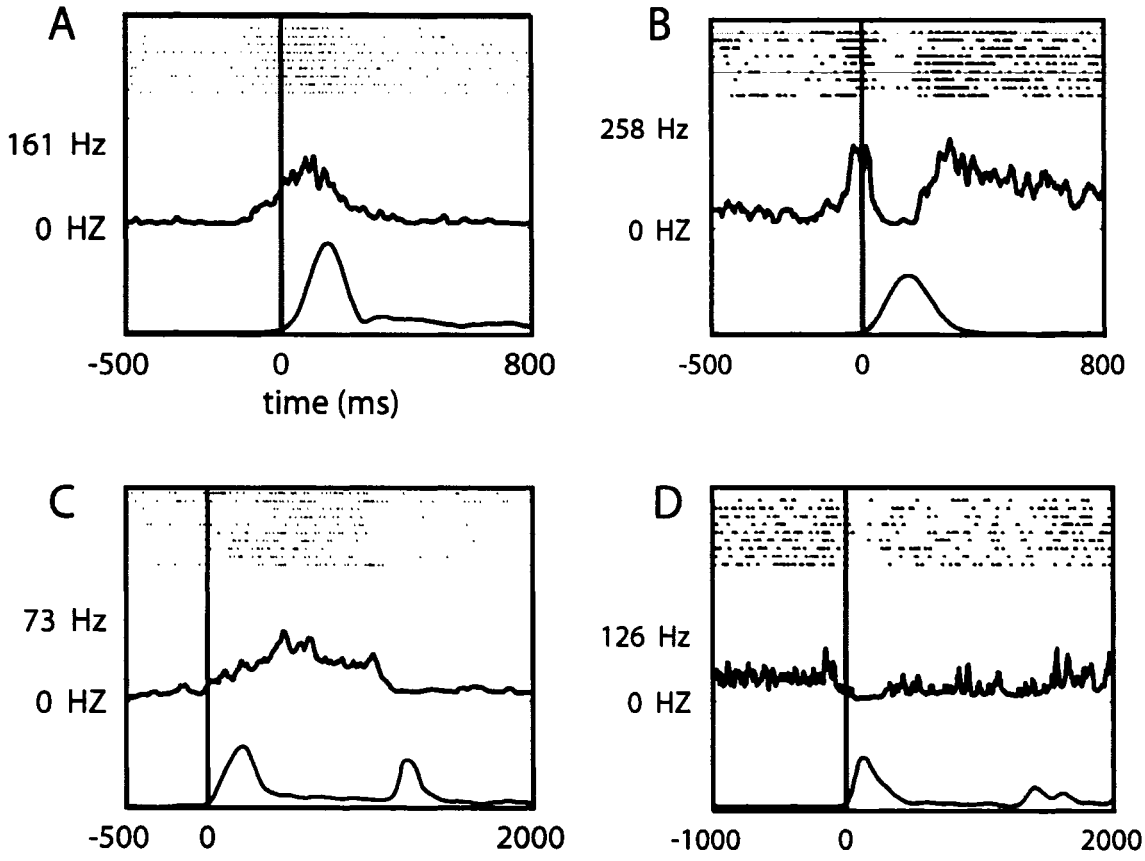

Figure 2.9. Examples of task-related modulation of neural activity in corticothalamic neurons. Each diagram shows a raster plot of action potentials in green at the top, with the averaged firing rate trace shown in blue and the average hand speed at the bottom in red. All traces are aligned on the onset of movement. The maximum instantaneous firing rate is shown to the left of each diagram. **A**, A neuron that shows a perimovement increase in activity. **B**, Neuron that exhibits a sharp burst of activity near the onset of movement, followed by sharp decrease in activity coincident with the peak velocity of movement. **C**, A neuron that shows a sustained increase in activity during the hold target period of the trial. **D**, A neuron that shows a pause in activity during the movement.

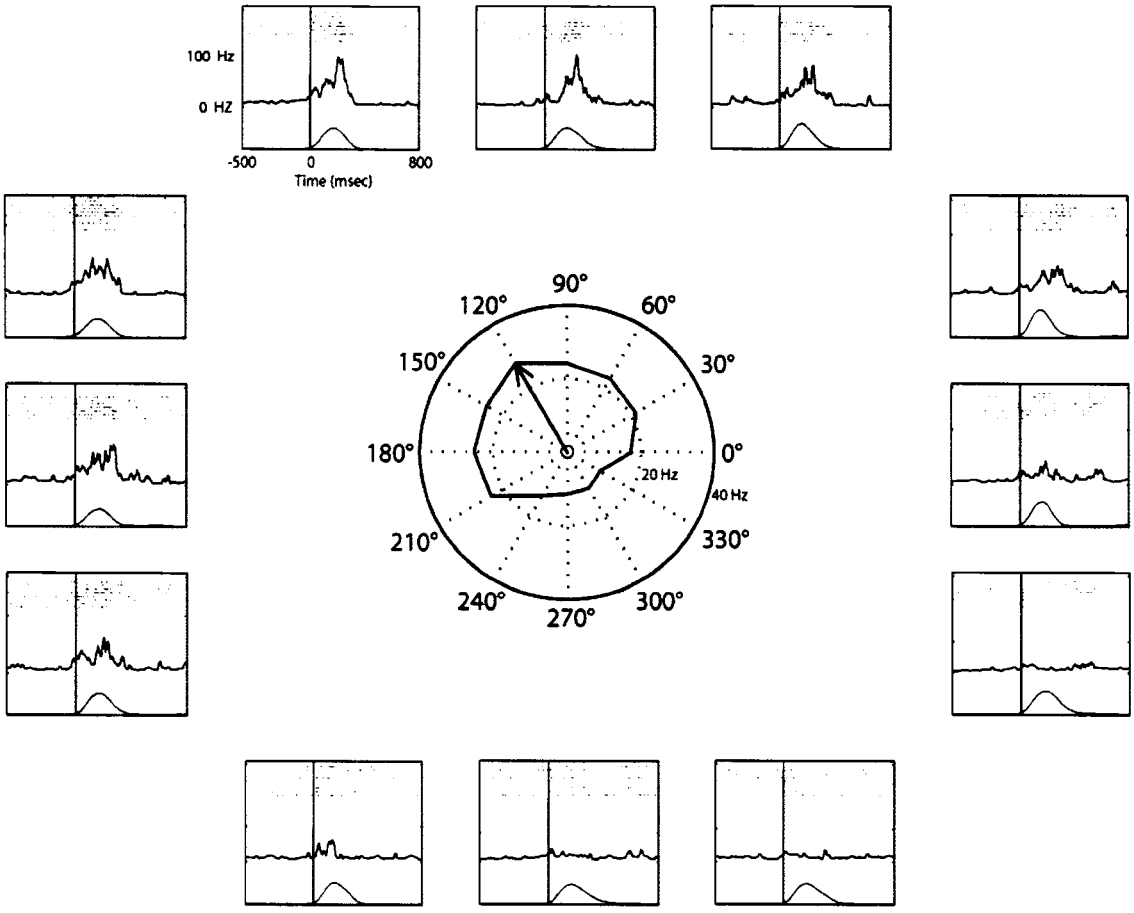

Figure 2.10. An example of a neuron with directionally-related modulation of activity. This neuron exhibits a large perimovement increase in activity when the monkey reaches for targets in the upper left portion of the workspace. For movements in the opposite directions, towards the lower right portion of the workspace, there is little modulation of neural activity. The mean neural activity associated with a 300ms window centered on the peak velocity of the movement in each direction is shown in polar plot form in the center of the figure. The arrow points in the direction of the target associated with the greatest modulation of neural activity.

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Chapter III

Neural Activity within Potential Corticothalamic Loops

Introduction

Primary motor cortex (M1) plays a key role in the control of voluntary movements. M1 receives considerable converging input from many cortical and subcortical regions, and it provides the largest contribution to the descending corticospinal tract, with some neurons synapsing directly onto α–motoneurons. Individual neurons in M1 do not reflect any single parameter of movement; instead, there is a range of information that is conveyed in the discharge patterns of individual neurons. While many neurons show activity that correlates with direction or force output (Evarts, 1968; Cheney and Fetz, 1980; Georgopoulos et al., 1982), others also express sensitivities to posture, position, velocity, acceleration, sensory input, target location, or some combination of these parameters (Evarts, 1968; Thach, 1978; Fetz, 1992; Ashe et al., 1993; Moran and Schwartz, 1999). This diversity is partly a reflection of the necessary complexity of the descending information targeting α and γ motor neurons, which includes information important for coordinating posture with

movement (Schepens and Drew, 2003) and for modulating spinal reflexes (Kaneko et al., 1987) and partly a reflection of the numerous inputs to M1.

The major subcortical source of input to M1 is the cerebellar-receiving (CR) portion of the thalamus, primarily the oral part of nucleus ventralis posterolateralis, VPLo (Dum et al., 2002; Sakai et al., 2002). This portion of the thalamus receives its major inputs from the deep cerebellar nuclei (Tracey et al., 1980; Kalil, 1981; Asanuma et al., 1983; Ilinsky et al., 1987) and from the motor cerebral cortex via reciprocal corticothalamic connections (Jones, 1985; Kultas-Ilinsky et al., 2003).

The incoming cerebellar fibers to thalamus form large secure synapses on proximal dendrites of thalamic relay cells (Sakai et al., 1996). The ultrastructure of these synapses suggests a highly secure transmission line, a notion supported by electrophysiological studies that show large "unitary" EPSPs in response to a single stimulation pulse in the cerebellum (Uno et al., 1970; Shinoda et al., 1985b). Such a synapse might fit the characteristics of a "driving input", in the terminology of Sherman (Sherman and Guillery, 1998, 2006).

The dentate's most numerous inputs are from the cortico-ponto-cerebellar projection which originates in the precentral cortex (Brodal, 1978; Schmahmann et al., 2004), and the interposed nuclei receive a large afferent input from peripheral somatosensory receptors via cerebellar cortex (Tolbert et al., 1978). Shinoda (Shinoda

et al., 1985a) demonstrated convergent inputs from the interpositus and the dentate nucleus at the level of the thalamus, providing one possible explanation for the observation that many neurons in the cerebellar- receiving thalamus have activity related both to movements and to sensory stimulation (Vitek et al., 1994).

In addition to its input from the cerebellum, the numerically major input to the CR thalamus comes from the cerebral cortex. As described in the previous chapter, there are two sets of corticothalamic axons. One has slowly-conducting axons, is believed to originate in cortical layer VI, and has little or no activity under behavioral conditions studied to date (Jones, 1985; Swadlow, 1994; Beloozerova et al., 2003a; Beloozerova et al., 2003b; Beloozerova et al., 2003c; Sirota et al., 2005; Sherman and Guillery, 2006). The second set of CT axons is rapidly-conducting, originates from cortical layer V, and has tonic activity that, in the arm area, changes with visually targeted arm movements (Jones, 1985; Sherman and Guillery, 2006)(Chapter II). These active CT axons are likely to be branches of corticospinal axons and, thus, to carry an efference copy of descending motor signals issued by M1 (Sherman and Koch, 1990; Bourassa and Deschenes, 1995; Bourassa et al., 1995; Levesque et al., 1996; Pare and Smith, 1996; Veinante et al., 2000).

The present study is designed to characterize the interaction between the motor thalamus, primarily the cerebellar-receiving region, and the primary motor cortex during a reaching task performed by primates. The activity of M1 neurons has been

studied extensively during reaching, and a broadly-tuned correlation between neural firing and the direction of hand movement is one of the most robust features identified, beginning with the studies of Georgopoulos and colleagues (Georgopoulos et al., 1982, 1983). Directional tuning has also been shown in cerebellar cells, where it tends to be wider than in cortical neurons, especially those with high background discharge rates and graded changes in rate for different movement directions (Fortier et al., 1993; Smith et al., 1993). The cerebellar and cortical cells selected for comparison, however, were selected only because they showed task-related changes in activity of at least 50% from the baseline. There was no direct attempt to identify whether the cerebellar and cortical neurons studied were in connected circuits.

The timing of corticothalamic and cerebellar thalamic actions at the thalamus also has not been compared in functionally connected cortical and thalamic neurons. Anderson and Turner (Anderson and Turner, 1991) did demonstrate, in a simple reaching task to a single target, that the discharge of most task-modulated cerebellar thalamic neurons was modulated before movement was initiated, and some changed their discharge prior to EMG modulation. Butler et al. (Butler et al., 1992) showed that, during ballistic wrist movements, many cerebellar thalamic neurons fired before EMG activity was initiated, and later, on average, than motor cortical neurons, Neither of these studies attempted to evaluate, however, whether the thalamic and cortical neurons were synaptically connected.

We have compared the directional tuning and task-related timing of the discharge of neurons in M1 and the CR thalamus that are potentially synaptically connected, as identified by antidromic and/or orthodromic activation from the thalamus. These comparisons, for corticothalamic (CT) and thalamocortical (TC) sets, allow us to estimate the degree to which corticothalamic activity shapes the discharge of thalamic neurons and how much the activity of cortical neurons is, in turn, shaped by thalamic activity.

Methods

Animals

Two juvenile male *Macaca fascicularis* monkeys (monkeys J and P) weighing 3.9 – 5.0 kg at the conclusion of these experiments were used. Subjects were obtained by the Washington National Primate Research Center (WaNPRC) at the University of Washington from its breeding colonies administered by Tulane University in Covington, Louisiana. Animals were cared for in accord with the Guiding Principles in the Care and Use of Animals (National Academy Press, 1996). All procedures were approved by the institutional animal care and use committee of the University of Washington. During the adaptation, training and work periods, animals were maintained on a food restriction protocol, using applesauce (up to 2 cups per day) as a reward to motivate behavior. Water was available in the home cage at all times, and

monkey chow and fruit were given on a daily basis. Weights were not allowed to drop below 90% of the original or expected weights.

Apparatus

The apparatus, task and surgical procedures have been described in detail (Chapter II). Briefly, the animal was perched in front of a half mirrored plexiglass sheet, onto which a virtual image of the task targets was projected. Below this was a digitizing pad that acted as the work surface for the monkey. The monkey's right hand, secured in a splint to minimize movements of the fingers and wrist, was free to move across the work surface, while the left hand was gently secured at the monkey's side. Embedded in the splint, under the monkey's palm, was a small magnetic coil. The location of this coil was tracked by the digitizing pad and used to monitor the position of the hand throughout the task.

The Visual Tempo System (V8.0; Reflective Computing) was used for behavioral control and data acquisition. Tempo acquired all data at a rate of 1 kHz. All signals were amplified, filtered, sorted on-line and stored using a Plexon data acquisition system.

Task

The monkeys were trained to make center-out arm movements to radially arranged targets in response to visual and auditory cues. All movement and hold periods during a trial were controlled as described in Chapter II. Rewards were delivered on a variable schedule at the end of successful trials.

Surgical Procedures

After the animal was trained to achieve success rates >90% in the task, two chambers were stereotaxically implanted in craniotomies over the left hemisphere allowing access to the arm-related areas of M1 and the motor-related nuclei of the thalamus. Chambers and nylon tubes placed horizontally to accommodate head stabilization bars were anchored with dental acrylic to titanium screws inserted into the skull.

Neural recording and stimulation

Neural recordings and stimulation were conducted using custom made, sharpened tungsten electrodes or commercially available stainless steel electrodes

(FHC, thalamus only) inserted into the brain through stainless steel cannulae used to penetrate the dura. Cortical electrodes were acutely inserted individually or as pairs and were positioned with a hydraulic microdrive (Trent Wells) attached to a custom built X-Y positioning stage that was mounted onto the monkey's recording chamber.

The majority of acute thalamic recording tracks were conducted using the same methods as for cortical tracts described above. For the remaining acute thalamic tracks and for all of the semi-chronic thalamic tracks, we used pairs of electrodes attached to screw-driven, grid-mounted miniature microdrives. Both tungsten and stainless steel microelectrodes were utilized during thalamic recording. The stainless steel microelectrodes were primarily used as low impedance chronic stimulating electrodes. However, with careful discrimination, we were able to record from a number of well-isolated thalamic neurons using these electrodes. Additional details about the recording procedure can be found in Chapter II.

Arm-related areas in M1 and anterior ventral thalamus (VPLo and VLo) were targeted for recording and stimulation. The recording locations in both the cortex and thalamus were determined using established physical and electrophysiological landmarks as described in Chapter II. After the initial mapping, we used thalamic microstimulation to orthodromically and antidromically activate neurons in cortex and to identify regions of the two structures that were potentially synaptically connected. Stimulation electrodes with impedances of 5 - 40 kΩ, were lowered into VPLo or VLo

using the screw-driven, grid-mounted microdrives. Electrode pairs were positioned so that the tips were located within, or bracketing, an area containing cells that showed arm-related or task-related activity, based on previous thalamic mapping tracks. The electrodes were spaced 2mm apart and were lowered until single or multiunit activity was observed that changed with movement of the arm during the task.

During search periods the stimulation paradigm for identification of antidromically activated neurons consisted of a single cathodal/anodal, biphasic stimulation pulse applied between two thalamic stimulating microelectrodes, with a pulse duration of 0.2 ms per phase and amplitudes ranging from 500 uA to 1 mA. Interspersed among the single search pulses were short trains of 3-12 pulses delivered at 120 or 240 Hz designed to elicit orthodromic responses or local field potentials in the cortex.

When a well-isolated cortical cell responded to a search pulse we conducted additional tests to distinguish antidromic from orthodromic activation. Neurons exhibiting 1) responses with constant latencies to stimulation (<0.2 ms jitter), 2) responses that reliably followed a high frequency stimulus train (3-6 pulses at 120 Hz), and when possible, 3) a positive collision test when stimulation was triggered by a spontaneous action potential, were considered corticothalamic neurons with antidromic responses to thalamic stimulation (Finlay et al., 1976; Fuller and Schlag, 1976). For antidromically- activated neurons, threshold currents (50% probability of activation)

were determined, and for latency and collision tests we stimulated with 140% of threshold current. The latency of an orthodromic or antidromic response to stimulation was measured as the time from stimulation delivery (onset of stimulation artifact) to the beginning of the evoked action potential. Neurons were classified as orthodromically activated if they failed the tests for antidromic activation but still responded to >50% of stimulus presentations with at least one spike (Swadlow, 1994). Neurons exhibiting a decrease in activity following stimulus delivery for any 2 consecutive 10ms bins, when compared to the 100 ms period prior to stimulation (ANOVA, $p<0.05$), were classified as orthodromically inhibited.

All signals were amplified, filtered and sorted on line using a Plexon data acquisition system and the TEMPO behavioral control and data acquisition system. Digitized waveforms, timestamps and behavioral data were saved to hard disk. Raw data were also stored on videotape using a pulse code modulator (Vetter 4000).

Data Analysis

Three periods from each task trial were identified based on behaviorally defined events. The control period began 200 ms after the monkey captured the central home target and consisted of the next 500 ms, during which the monkey continued to hold the home target. A perimovement period of 300 ms was centered on the occurrence of the

peak velocity of the reaching movement. Finally, a reward period of 300ms began with the delivery of reward. Movement onset was defined as the first 10 ms bin during which a sustained increase in hand velocity occurred, based on threshold and duration criteria, and the onset of the change in neural activity was defined as occurring at the beginning of the first of 3 consecutive 10 ms bins with discharge rates differing from the baseline rate (ANOVA, $P<0.01$).

Neurons that showed statistically significant movement-related changes in activity during the perimovement period compared with the control period were included in this analysis (t-test, $P<0.01$). These cells were then tested for movement direction related variations in activity with a regression analysis to a tuning function based on the von Mises, or circular normal, distribution (equation 1).

$$d(\theta) = b + k \exp(\kappa \cos(\theta - \mu)) \quad (1)$$

This function reaches a maximal discharge rate $d(\theta)$ at $\theta = \mu$, thus making μ the preferred direction for a particular cell. As the parameter κ increases in value, the tuning curve acquires a more narrow shape, and as κ becomes very small and approaches zero, the function degenerates into a standard cosine tuning function. The parameter b represents the baseline discharge rate and k is a scaling factor. The von Mises tuning function provides a significant advantage over the standard cosine tuning function as it can distinguish between a very sharply tuned neuron with a narrow tuning curve and a

broadly tuned neuron with a wide (cosine) tuning curve. In order to compare tuning curves, we used the standard quantitative measure of the breadth of directional tuning, the half-width (σ). This is a measure, in degrees, of half of the width of the tuning curve that falls above the half maximal normalized discharge rate. A standard cosine function has a half width of $\sigma = 90°$. We compared the tuning curves and half widths (σ) across populations and within sets of neurons from potentially connected regions of cortex and thalamus.

We used the measure of circular variance (S_n), as defined by Mardia (Mardia, 1972), to quantify the dispersion of preferred directions within sets of neurons. Highly spread out observations have variances approaching one, while clustered observations have a circular variance close to zero. The Rayleigh test for circular uniformity was also used to describe the distribution of preferred directions within sets.

To increase the power of our statistical tests, we pooled the preferred direction differences from the individual sets. To determine preferred direction differences we found the absolute value of the smallest angle between the preferred directions of any two neurons within a set. Comparison of the preferred direction difference distributions between categories was performed with a one-tailed two sample Kolmogorov-Smirnov test (Ben-Shaul et al., 2003).

Results

Potentially connected sets of cortical and thalamic neurons

We report here on 111 groups of potentially connected neurons (potential sets) in motor thalamus (VPLo) and primary motor cortex from two monkeys. These groups are of two types, based on whether the cortical neuron was activated antidromically (CT cortical neurons) or activated or inhibited orthodromically (TC cortical neurons) from the thalamus. The cortical neurons in both types of potential sets exhibited spontaneous activity, and the thalamic neurons of the sets included those located in the tracks of either of the thalamic stimulation electrode and within 50 microns of the depth from which the cortical cells were activated. CT neurons that did not exhibit significant spontaneous activity (see Chapter II) were not included in this analysis.

A total of 49 potential CT sets was studied. These were composed of 81 antidromically activated cortical neurons with spontaneous activity and the 112 thalamic neurons that were located within 50 microns of the stimulation sites (2 sites for each pair of stimulation electrodes) that produced the antidromic cortical activity. The number of antidromically activated cortical neurons in a CT set ranged from 1 to 3, and the number of thalamic neurons in a CT set (i.e., within 50 u of the depth of thalamic stimulation), ranged from 1 to 4.

The 62 potential thalamocortical (TC) sets studied included cortical neurons activated orthodromically at a short (monosynaptic) latency (<3 ms) by thalamic stimulation. These 62 sets were composed of 124 orthodromically activated or inhibited cortical neurons and the 77 thalamic neurons near the stimulation sites. Of the orthodromically identified neurons, 116 were activated by thalamic stimulation and 8 showed inhibitory responses to thalamic stimulation. All cortical neurons activated orthodromically from the same stimulation site were grouped in a potential set. TC sets included 1 to 2 orthodromically activated cortical neurons and 1 to 5 thalamic neurons.

Stimulation at 27 thalamic sites elicited both orthodromic and antidromic responses from cortical penetrations. However, no cortical neurons showed both types of activation with the stimulus parameters that we used. This meant that, based on the criteria for defining TC and CT sets, the cortical neurons activated from these sites were associated with only a single CT or TC grouping. However, 48 thalamic neurons located near these stimulation sites were included in both CT and TC sets because cortical neurons excited from that thalamic stimulation site were excited either orthodromically or antidromically. These thalamic neurons are therefore represented multiple times for analysis.

Cortical extent of potential sets

The cortical neurons in a potential set extended over a very restricted region of cortex, with CT sets including a smaller cortical area than TC sets (see Chapter II, Antidromic response fields vs. orthodromic response fields).

The depth at which the cortical neurons were recorded also differed for the two groups. Orthodromically activated neurons were found more superficially in a recording tract than the antidromically identified cells (1310 microns vs 1615 microns, ANOVA, $p<0.01$). This, plus the fact that no cortical neurons were activated both antidromically and orthodromically at short latency suggests that we recorded from 2 different populations of cortical neurons, with orthodromically activated cells potentially located in layer III and antidromically activated cells in layer V.

If the potential sets really do include cortical and thalamic neurons that are synaptically connected and have activity related to arm movement, then one might predict that they would show similar preferred movement directions. To test this, we compared the directional characteristics of task-related activity of neurons within and between TC and CT potential sets.

Directional tuning of cortical and thalamic activity

CT sets.

The preferred directions for movement-related changes in activity of thalamic and cortical neurons in potential sets were similar, as predicted if they truly were connected. The preferred targets and preferred directions for each cell in a potential CT TC set were determined from data derived during movements in 8 or 12 directions, as shown in Figures 3.1 and 3.2. Fig. 3.1 shows the neural activity for the 2 thalamic and 2 cortical neurons in a potential CT set, while Figure 3.2 shows the neural activity associated with the 2 cortical and 2 thalamic neurons from a representative TC set. In each case, the polar plot in the center of the panel shows the mean perimovement activity for each direction, with the arrow indicating the target direction for which the change in activity was greatest.

Figure 3.1

The cortical CT cell in Panel A (Figure 3.1.1) exhibited the largest modulations during movements to targets on the right side of the workspace, with the preferred

target direction of 0°. The increase in activity led the onset of movement to the cell's preferred target by 80 ms. The mean change in the perimovement firing rate for movements in the preferred direction was 37 Hz. The CT cortical neuron in Figure 3.1.2 shows a mean increase in activity of 19 Hz with a latency of -210ms relative to the movement onset to the preferred target of 0°.

A preferred direction that was not constrained to one of the target directions could be derived from the fit to the von Mises function (Amirikian and Georgopoulos, 2000) (see Fig. 3.7 for the fits associated with the data included in Figure 3.1). When the perimovement activity across directions for the activity of the cell shown in Fig 3.1.1 was fit by the von Mises function (Fig 3.7A) it showed a good fit ($R^2 = 0.95$) and a predicted preferred direction of 2° for this cell. The von Mises fit for cortical neuron B, shown in Figure 3.7B, predicts a preferred direction of 336° ($R^2 = 0.91$).

In comparison, Figs 3.13 and 3.1.4 show the plots for the thalamic neurons from the same CT set. The cell in Fig 3.1C shows an increase in perimovement activity that precedes the onset of movement to the preferred target (90°) by 70 ms. The von Mises tuning curve for this neuron, shown in Fig 3.7C, predicts a PD of 74° ($R^2 = 0.77$). The second thalamic neuron in the CT set, shown in Fig 3.1D exhibits a sharp increase in activity with a latency of 50ms, during movements towards the preferred target (330°). Fig 3.7D shows the von Mises fit for this cell, with a predicted PD of 345° ($R^2 = 0.46$).

TC sets

Figure 3.2

Fig 3.2 shows the directional activity of the 4 neurons from a single TC set. In Fig 3.2.1, cortical neuron A shows an increase in activity that precedes the movement (mean -187 ms), has a preferred target direction of 240° and a von Mises determined predicted PD of 227°. The second cortical neuron, in Fig 3.2.2, shows an increase in activity that precedes the start of the movement by a smaller amount (mean 42 ms), and has a preferred target direction of 180°. Its von Mises determined PD is 185°. The potentially linked thalamic neurons are shown in Figs 3.2.3 and 3.2.4. Thalamic neuron A (Fig. 3.2.3) showed a latency of -17ms for movements towards the preferred target (180°) and had a von Mises fit PD of 125° (R^2 = 0.87). Thalamic neuron 2 (fig. 3.2.4) had a latency of -101ms with movements towards the preferred target direction of 240° and had a von Mises fit PD of 195° (R^2 = .59).

Figure 3.3

The preferred directions derived from the von Mises fit for the cells studied in Fig. 3.1 are shown as a polar plot (cortical = blue, thalamic = red) in Fig. 3.3A. The differences between the preferred directions for the 4 neurons are shown as a histogram in the lower panel. The preferred directions of these neurons fall within a 98° range around a mean movement angle of 6°, with the preferred directions of 3 of the 4 neurons falling within 26°. The dispersion of these directions is low (S_n =0.2), and the Rayleigh test for circular uniformity shows that this collection of directions is unlikely to be random (p=0.07).

The von Mises-derived preferred directions for the neurons in the TC set from Figure 3.2 are shown in the polar plot of Fig. 3.3B, and the differences between their PDs area shown in the histogram below it (cortical = blue and thalamic = red). The preferred directions fall within a range of 102°, and 3 of the 4 lie within 60° (2 targets) with a circular mean of 185° (S_n =.19, Rayleigh p=0.07).

Comparison of preferred direction differences across populations

The dispersion of directions within the individual sets described above is relatively narrow, but the small number of cells within a set keeps the statistical power of the Raleigh test very low. To overcome this, we focused on the differences between preferred directions (lower panels of Fig. 3.3) and pooled the data to analyze the overall

dispersion across the population. Independent preferred directions would yield a uniform distribution of differences across the range of 0-180°. The population data in Figure 3.4 show that the distributions are heavily skewed towards small differences between directions, and each subpopulation significantly differs from a uniform distribution (t-test, $p<0.01$) with the exception of the thalamic/thalamic differences from the TC sets (t-test, $p=0.18$). This means that most potentially connected cortical and thalamic neurons defined by stimulation in the thalamus also had PDs within at least the same quadrant of the work space.

We analyzed the differences in preferred directions across subcategories of neurons to identify possible differences in alignment patterns. For example, did the antidromically activated cortical neurons have more closely aligned PDs than the recipient thalamic neurons within CT sets? The breakdown of neurons into subpopulations (cortical-cortical, thalamic-thalamic and cortical-thalamic) allowed pairwise PD difference distribution comparisons across categories for a total of 9 comparisons. There was no pattern in the distribution of orthodromically activated TC neurons vs. orthodromically inhibited TC neurons, so both types of TC cortical neurons grouped together. We compared categories within each set type (cortical/cortical vs. thalamic/thalamic vs. cortical/thalamic X 2), and we compared similar categories across sets (CT cortical/cortical vs. TC cortical/cortical etc.). Only the TC t/t distribution showed a tendency to differ from the other distributions, but because of its small sample size, the tendency did not reach a significant level for any comparison.

Figure 3.4

Timing of cortical and thalamic activity during movement

To compare the timing of the neural activity of cortical and thalamic neurons we measured the latency of perimovement activity within potential sets relative to the onset of movement to targets closest to the preferred direction (the preferred target). As shown in Fig 3.5A, in CT sets, the mean onset latencies of cortical activity (-120 ms ± 23 ms) preceded those of thalamic neurons (-95 ms ± 46 ms), and this difference was significant (ANOVA, $p<0.01$). In fact, all CT cortical neurons began their discharge before the initiation of movement in the neuron's preferred direction. In contrast, in the TC sets (Fig 3.5 B), the mean onset latencies of the cortical and thalamic neurons did not show significant differences, although the activity of the thalamic neurons showed a small tendency to precede that of the cortical neurons (cortical latency, mean -96 ms ± 29 ms; thalamic latency, mean -102 ms ± 33 ms, ANOVA, $p= 0.19$) (Fig 3.5B). A small number of neurons in TC sets, both cortical and thalamic, did not begin their discharge until after initiation of movement in the preferred direction.

Figure 3.5

Consistent with the data described above, the onset latencies of the cortical neurons also differed when those in the two classifications (TC vs. CT) were compared directly, as shown in Fig 3.5C. The movement-related activity of cortical CT cells preceded that of cortical TC neurons (-120ms vs. -96ms, ANOVA, $p < 0.01$). The onset latencies of the thalamic neurons (Fig. 3.5D) did not differ across classification type (Fig 3.5D, ANOVA, $p = .36$). This result is not surprising, as these two populations each included the 48 thalamic neurons that were part of both CT and TC sets.

Although as a whole, the cortical CT neurons change their activity earlier than the thalamic neurons or the TC cortical neurons synaptically activated from the thalamus, there is considerable overlap. It is of interest, then, to compare the timing of activity within individual sets, which should have a higher probability of being connected. In Figure 3.6 each set is represented by a single point. The mean latency of the cortical neurons within a set is plotted against the mean latency of the thalamic neurons within that set. The latencies are taken from the target direction that lies closest to the angular mean of the preferred directions of all the neurons within the set, so that the latencies compared are all for movements to the *same target direction.* The preferred target of all neurons within any set was within one target of the mean

preferred direction of that set 74% of the time. Points located below the dotted line represent sets with a mean onset of cortical activity that precedes thalamic activity, while points above the line represent sets with mean thalamic activity that precedes the mean cortical activity. The CT sets, (Panel A) show a significant tendency ($p<0.05$) for the cortical activity to lead the thalamic activity, while the TC sets show no such relationship.

Figure 3.6

Width of tuning curves within sets

The width of the directional tuning curves, as determined by the von Mises function, allowed us to compare the tuning for cortical and thalamic neurons within each set and within the total sample of TC and CT sets. There were significant differences in the sharpness of directional tuning when cortical and thalamic tuning curves were compared within both types of sets.

Figure 3.7

Figure 3.7 shows the tuning curves fit to the data for the CT cells of Figure 3.1. In each case, the red curve is the fit to the von Mises function and the blue curve is the cosine fit (which has a fixed half width of 90°). In both cortical cells of the CT set, but especially in cortical cell A, the tuning determined by the von Mises function has a smaller half width (σ for each neuron: A = 41.5°, B = 79.5°) than the 90° of the cosine function, while the cosine and von Mises tuning functions for the thalamic neurons are nearly identical.

The tuning curves for the cortical and thalamic neurons of the TC set studied in Fig 3.2 are compared in Figure 3.8. Both cortical neurons, but especially cortical cell B, show narrower tuning than the thalamic neurons in the set (cortical σ = 75.5° and 28.5°, thalamic σ = 90° and 90°).

Figure 3.8

In Figure 3.9A and B the *population* tuning curves fit by the von Mises function are shown for the CT sets (A) and the TC sets (B). The CT set cortical population tuning curve (blue) shows a mean half width σ of 64° (indicated by dotted line) and a mean change in firing rate of 32 Hz, compared to baseline, when the animal reached towards the preferred target direction. Overlaid on the same graph, the thalamic population tuning curve (red) shows a half width σ of 84° and a mean peak change in

firing rate of 58 Hz for movements towards the preferred target. The difference in half widths of raw discharge rate across populations is highly significant (ANOVA, $p<0.001$), as is the difference in depth of modulation (ANOVA, $p<0.001$).

Figure 3.9

The width of the population tuning curve for thalamic neurons in TC sets (Figure 3.9B) was also wider than it was for cortical cells. As shown in Figure 3.9B, the TC cortical population curve (blue) has a mean half width σ of 71° and a mean peak change in firing rate from baseline of 26 Hz when the animal reached towards the preferred direction. The TC thalamic population curve (red) has a half width σ of 86° and a mean peak change in firing rate of 52 Hz. Differences in half widths (ANOVA, $p<0.001$) and depth of modulation (ANOVA, $p<0.001$) of the TC populations are highly significant.

If the cortical and thalamic neurons in the potential sets studied really are connected, then the narrower tuning curves for cortical neurons in both types of potential sets implies a sharpening influence at the cortex that is added to the thalamocortical action and removed or counteracted in the corticothalamic action.

Discussion

This work was designed to study the relationships between the cerebellar receiving motor thalamus and the primary motor cortex by comparing the activity of potentially-connected neurons from each area. Issues that hinge on this relationship are: What is the nature of the driving afferents to the motor thalamus? In addition to the well-characterized input from the deep nuclei of the cerebellum, is there a driving input from motor cortex? If so, what contribution does this projection make to the activity of thalamic relay neurons in the motor thalamus? Is the motor thalamus under cortical control or cerebellar control? How does the ascending cerebello-thalamo-cortical projection in turn influence the output of the motor cortex?

Sherman and Guillery (Sherman and Guillery, 1996, 1998) have divided thalamic relays into first-order (sensory) and higher-order (association) relays. First-order relays represent the first transmission to cortex of a particular type of information from the periphery, and higher-order relays serve to transmit information between cortical areas via a cortico-thalamo-cortical route. In their terminology, drivers are the source of the essential pattern of activity in the thalamic neurons, whereas modulators control the effectiveness of the drivers. Anatomically, there is strong evidence that the Type I axon terminations in the thalamus, which have small boutons and synapse on

distal dendrites, arise from pyramidal cells of layer VI and act as modulators(Rockland, 1996; Rouiller and Welker, 2000). Type II axons terminate in large boutons on proximal dendrites and arise from subcortical sources or from layer V cortical neurons and would be expected to act as drivers (Gilbert and Kelly, 1975; Deschenes et al., 1994; Bourassa and Deschenes, 1995; Ojima et al., 1996).

The thalamic motor nuclei, including the pallidal receiving and cerebellar receiving thalamus, defy easy categorization as first or higher-order nuclei. In particular, based primarily on anatomical studies, the cerebellar receiving thalamus has two sets of driving inputs, one from the layer V corticothalamic projection and one ascending from the deep cerebellar nuclei. Both projections end in Type II axons with large terminations on proximal dendrites, suggesting that the cerebellar receiving thalamus is influenced by two driving input populations. One intracellular recording study showed that thalamic relay neurons exhibited remarkably similar synaptic activation properties from cerebellar and cortical afferents (Sawyer et al., 1994), and our recent study suggests that the layer V corticothalamic projection carries M1 like activity and is a potential driving input to the motor thalamus (Chapter II).

In our present study, we identified M1 neurons that we could or could not demonstrate sent axons to the cerebellar-receiving thalamus, and we compared their activity to their potential thalamic target neurons (in CT sets) or to thalamic neurons that may have provided their thalamocortical input (in TC sets). Although we could not

prove that the neurons grouped in potential sets were, in fact, synaptically connected, we increased the probability of studying cells in interconnected circuits based on the fact that their axons (or cell bodies) were close enough to our thalamic stimulating electrodes to be activated (cortical cells in CT sets; thalamic cells in TC sets) and the thalamic neurons whose activity we recorded were close to those same stimulating electrodes. The probability that the cortical and thalamic neurons grouped in sets actually were connected was increased by the finding that they had preferred directions within a relatively narrow range. Within both types of sets, there was a highly non-random relationship among the preferred directions of grouped neurons. This was not a result of some preferred directions being heavily represented in our sample population or in the limited regions of cortex and thalamus that we recorded from. Across our entire population of ungrouped, sampled neurons we found a uniform distribution of preferred directions. Thus, we take the directional alignment within sets, along with the latency patterns and stimulation responses, as evidence that our sets represent groups of neurons with a high probability of being synaptically connected.

Cortical neurons included in CT groups showed antidromic responses to thalamic stimulation and were presumed to be corticothalamic neurons that project to, or through, the neurons in the stimulated region of thalamus. Based on electrophysiological characteristics (short latency antidromic response to thalamic stimulation and a high level of spontaneous activity) and the depths within a recording

tract at which these neurons were found, we assumed that these neurons originated in cortical layer V (see Chapter II for further discussion of this classification).

The cortical neurons that were included in TC groups showed short latency orthodromic stimulation effects and were presumed to receive a projection from neurons in the stimulated region of thalamus. These neurons were primarily found superficial to antidromically activated neurons, which suggests that they are located in cortical layers I or III. This is consistent with other reports that the thalamocortical projection from VA and VL terminates most densely in layers I and III, with a more sparse projection to layers V and VI (McFarland and Haber, 2002).

Six percent (8/124) of the TC cortical neurons exhibited orthodromic inhibition in response to thalamic stimulation. Apart from the difference in response to thalamic stimulation, orthodromically activated and inhibited cortical neurons were indistinguishable. Orthodromic inhibition could be produced via a disynaptic pathway including activation of a thalamic or cortical interneuron. We only included neurons that showed short latency orthodromic responses (<3ms) in our analysis, so many of the cortical neurons that showed longer latency orthodromic inhibition were excluded. It might be expected that TC neurons exhibiting orthodromic inhibition would have different PD distributions than orthodromically activated TC neurons. However, our study did not include enough orthodromically inhibited neurons to address this question.

Possible Cortical TC neuron activation through corticothalamic collaterals

It does remain possible that the activation effect witnessed in cortical TC neurons, which we classified as orthodromic activation, occurred via collaterals of antidromically activated corticothalamic neurons. While we cannot completely rule out this possibility, there are several reasons to believe that the cortical TC neurons were activated orthodromically.

It is questionable whether an antidromically evoked action potential could reliably invade a collateral because of the increase in membrane area and corresponding decrease in input resistance that is likely to occur at a branch point (Swadlow et al., 1980). However, if the action potential did successfully invade the collateral, it would be expected to travel at slower speeds than it does along the main branch of the axon (Nowak et al., 1997). Since we set an activation latency of <3ms as a criteria for inclusion in our analysis, it is unlikely that a cortical neurons could be activated quickly enough along a slowly conduction collateral to be included in our analysis.

Other studies also suggest that activation via collaterals of corticothalamic neurons is unlikely to occur. It is possible to directly test if V1 neurons are orthodromically activated or activated via corticothalamic collaterals during stimulation in the LGN. If V1 neurons are also activated at an appropriate disynaptic latency by stimulation of the optic tract, then they can only be activated by LGN efferents,

confirming that they were orthodromically activated by LGN stimulation. In the several studies in which this test was performed, virtually every V1 neuron that was activated at a short latency from the LGN was also activated from the optic tract, suggesting that very little activation of cortical neurons occurs via collaterals of corticothalamic neurons (Toyama et al., 1974; Singer et al., 1975; Bullier and Henry, 1979; Ferster and Lindstrom, 1983). Additionally, in M1, it has been shown that the excitatory postsynaptic potentials that arise from collaterals of pyramidal tract neurons are relatively weak and unlikely to evoke action potentials (Deschenes et al., 1979b).

Lack of orthodromic and antidromic activation in single neurons

It is interesting to note that we saw no neurons that were activated both orthodromically and antidromically. Many studies have reported that layer V motor cortex corticofugal neurons receive monosynaptic excitatory input from the VA-VL thalamic nuclei (Yoshida et al., 1966; Deschenes et al., 1979a; Shinoda et al., 1985a; Futami et al., 1986), and Na has reported that orthodromic activation from the thalamus produces short latency EPSPs in some antidromically identified CT neurons in layers V and VI of the motor cortex in anesthetized cat (Na et al., 1997). In our study, if a cortical neuron were activated both orthodromically and antidromically and the orthodromic latency was less than the antidromic, the antidromic spike would not be seen due to collision in the axon with the spike evoked orthodromically. This

ambiguity prevents us from making a definitive statement concerning overlap between the TC and CT cortical population, but the stimulation responses, latency and depth data support the idea that these cortical groups are distinct populations. If antidromic spikes were abolished by collision with spikes produced orthodromically, it would mean that our CT population was lacking some of its more slowly conducting neurons.

Latency of movement-related activity

Within CT sets, the movement-related activity of cortical neurons showed a significant tendency to lead that of the thalamic neurons, while in TC sets, no such relationship exists. In fact, cortical CT neurons fired, on average, earlier than all other classifications of neurons. If these CT neurons carry an efference copy, this signal from cortex arrives at the thalamus early enough to interact in a significant way to influence thalamocortical discharge related to the movement.

Directional tuning

The tendency of cortical neurons to show sharpened tuning when compared to thalamic neurons implies that the sharpening is occurring at the cortical level. This is

also consistent with the earlier comparison of the sector widths of cerebral and cerebellar neurons as described by Fortier et al. (Fortier et al., 1993).

Early studies that established the directional tuning of M1 discharge used a cosine function, which has a fixed half-width of 90 deg (Mardia, 1972; Georgopoulos et al., 1982; Schwartz, 1992). To determine how sharp the focusing effect is, however, another quantitative method must be used. We constructed our tuning curves by fitting our neural data to a von Mises function, as was done for cortical neurons by Amirikian and Geogopoulos (Amirikian and Georgopoulos, 2000). This function generally produced a much better fit than did the cosine function, as shown in Figures 3.7 and 3.8. We used the half width measurement (σ) to compare the breadth of tuning within sets and across populations, and found that cortical neurons from both classifications showed sharper tuning than thalamic neurons.

Also, based on the latency data showing that the CT cortical neurons modulate their activity earlier than thalamic neurons, it is unlikely that the sharpening is occurring as a result of the thalamic input. Instead, other inputs to M1, or processing within M1 must be responsible for the sharpening of the directional tuning of cortical neurons. The exact nature of this phenomenon remains to be addressed.

Corticothalamic projection

Our results show that the layer V corticothalamic projection to the cerebellar receiving nuclei of the motor thalamus carries M1-like activity that is sharply tuned and modulates prior to the onset of a movement. However, the thalamic neurons that presumably receive this input show modulation later and are more broadly tuned than these cortical neurons. In a study comparing cerebellar and motor cortical activity during a reaching task in monkey, Fortier et al. showed that neurons from the cerebellar cortex and deep nuclei (interpositus and dentate) were more broadly tuned than neurons in the motor cortex (Fortier et al., 1993). In one of the few studies including recordings from cerebellar receiving thalamus and motor cortex, it was shown that motor cortical neurons exhibited phasic changes in activity earlier than neurons in cerebellar receiving thalamus, and that the activity of both was modulated prior to forearm EMG changes (Butler et al., 1992). These studies, along with our results, provide evidence that thalamic neurons are more strongly influenced by cerebellar input than by corticothalamic layer V input.

Some current models propose that activity in the cerebello-thalamo-cortical projection is related to movement duration (Ivanusic et al., 2005) and that changes in cerebellar-receiving thalamic activity might influence the duration or timing of motor cortical neurons (Meyer-Lohmann et al., 1977; Hore and Flament, 1988). In the context of these models, the layer V corticothalamic projection, carrying an efferent copy of

current M1 output, could be an appropriate gatekeeper for ascending cerebellar information related to the duration or coordination of an action. In this role, the modulation of activity of the layer V corticothalamic neurons would not drive the activity of thalamic neurons, but instead would serve to regulate the timing of the passage of cerebellar information destined for the cortex. Another function of the efferent copy signal in the thalamus could be to suppress the incoming activity to which a cortical response has already been formed and sent to the spinal cord. This could be accomplished through the activation of thalamic inhibitory interneurons.

A further possible action of the layer V corticothalamic projection is to induce change at the level of the thalamic synapse. Aumann and Horne (Aumann and Horne, 1999) have shown that after adaptation to a novel load, rats showed an increase in the number of docked vesicles at cerebellothalamic dendritic zones. In a subsequent study, Aumann, et al., showed that rat cerebellothalamic synapses are capable of expressing LTP *in vitro* (Aumann et al., 2000). If this reorganization or strengthening of cerebellothalamic synapses requires task-related inputs, then in an *in vivo* situation, the layer V corticothalamic projection is well situated to provide the neural activity necessary to induce the longer term ultrastructural changes or the short term LTP documented in these studies. In this role, the layer V corticothalamic projection may act as a modulator, working to strengthen or weaken synapses throughout the thalamus. In fact, Krupa et al., (1999) have shown that plasticity of receptive fields in the

somatosensory thalamus induced by block of a peripheral nerve is reduced if the somatosensory cortex is inactivated (Krupa et al., 1999).

Summary

In summary, we have shown that potentially anatomically connected sets of cortical and thalamic neurons can be identified in the motor system of the primate. We categorized these groups as CT or TC sets, based on the responses of cortical neurons to thalamic stimulation. TC sets, defined by the orthodromic activation of cortical neurons, included cortical and thalamic neurons that exhibited similar latencies relative to movements, but the cortical neurons showed sharper directional tuning characteristics. CT sets included cortical and thalamic neurons that differed significantly in both the timing and the spatial focusing of their activity during reaching, with the presumed layer V corticothalamic neurons firing earlier and exhibiting sharper tuning than their grouped thalamic neurons.

These results suggest that cortical input to the thalamus, potentially an efferent copy of corticospinal output, is available early enough to influence thalamocortical activity. It leaves open the possibility that this projection is a 'driving' input of the motor thalamus. The spatial tuning of thalamocortical activity, however, may be more

heavily influenced by input from the cerebellum than from the motor cortex, and MI spatial tuning may be sharpened by local circuitry at the cerebral cortex.

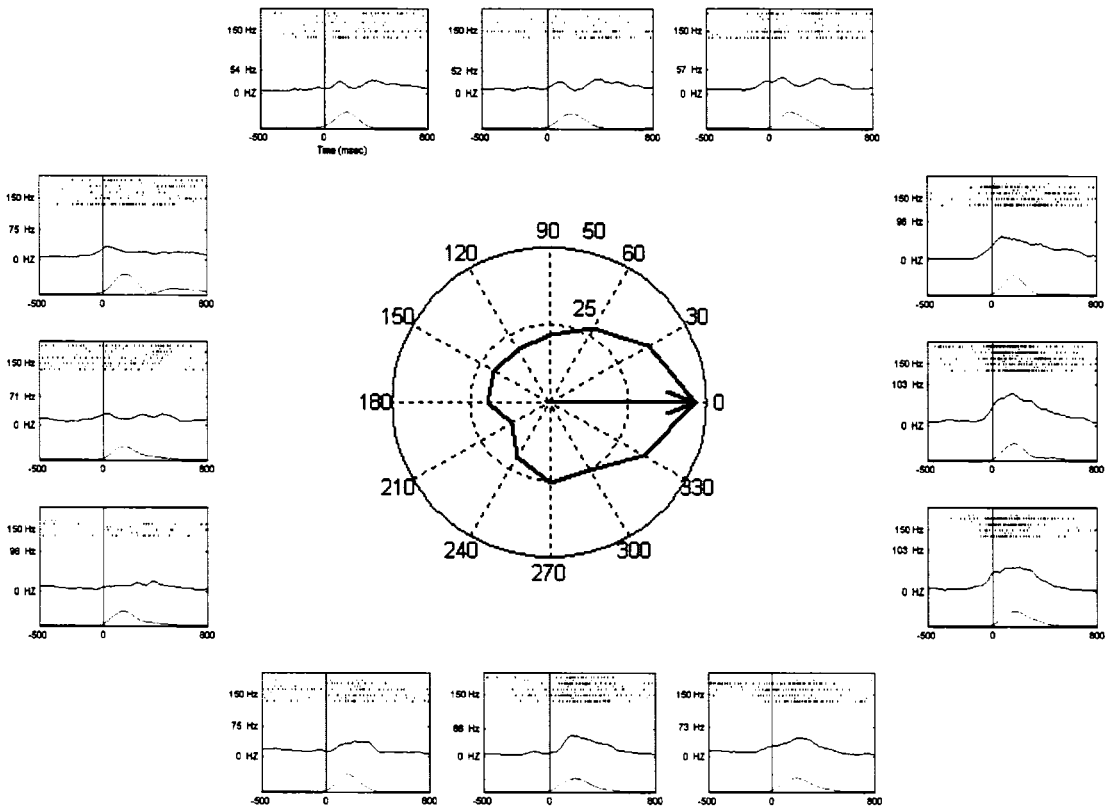


Figure 3.1.1. Neural activity of cortical neuron **A** from a potential CT set. The monkey was engaged in a visually guided reaching task to one of twelve targets arranged radially around a central hold point. Cortical neurons included in CT sets were antidromically activated by thalamic stimulation, and thalamic neurons in the same CT set were located within 50 μm of the thalamic stimulation site from which the antidromic activation was elicited. Data from trials associated with movements towards a single target are grouped into the individual boxes above. Each box shows a raster plot of action potentials in green at the top, with the average firing rate trace shown in blue and the average hand speed at the bottom in red. All traces are aligned on the onset of movement. The maximum instantaneous firing rate is labeled to the left of each diagram. The mean neural activity associated with a 300ms window centered on the peak velocity of the movement in each direction is shown in polar plot form in the center of the figure. The arrow points in the direction of the target associated with the greatest modulation of neural activity.

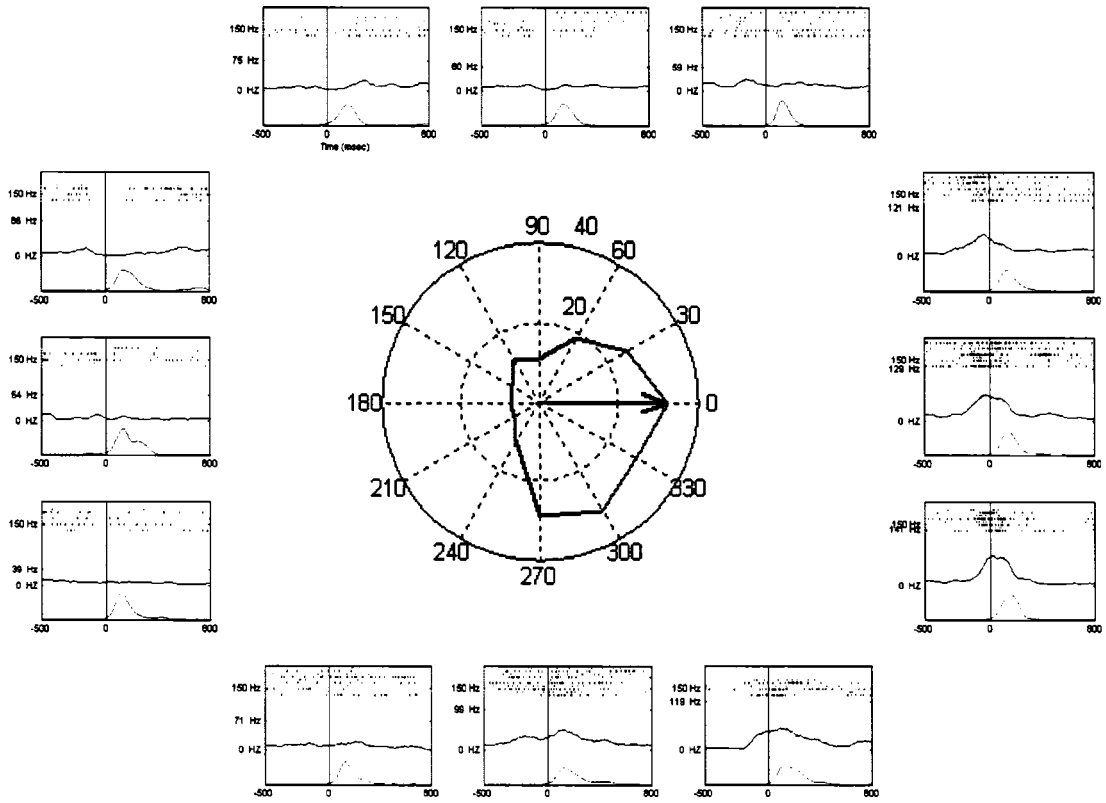


Figure 3.1.2. CT set, cortical neuron **B**.

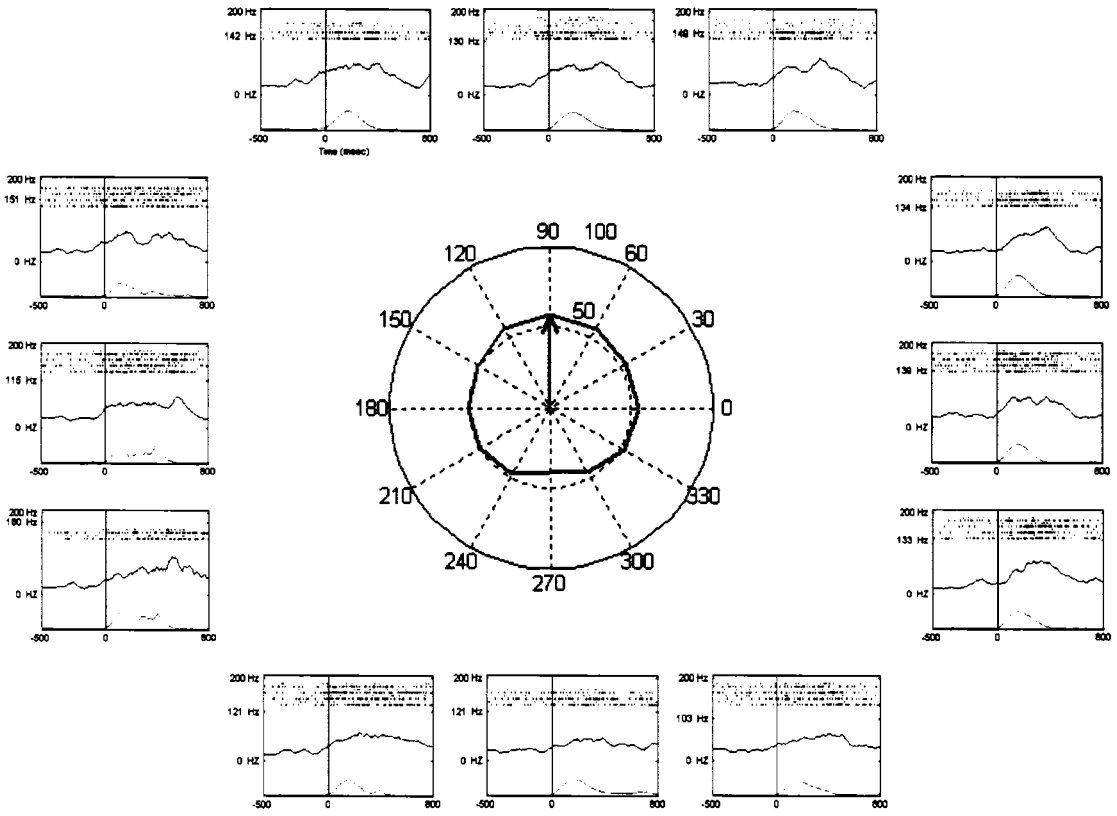


Figure 3.1.3. CT set, thalamic neuron **A.**

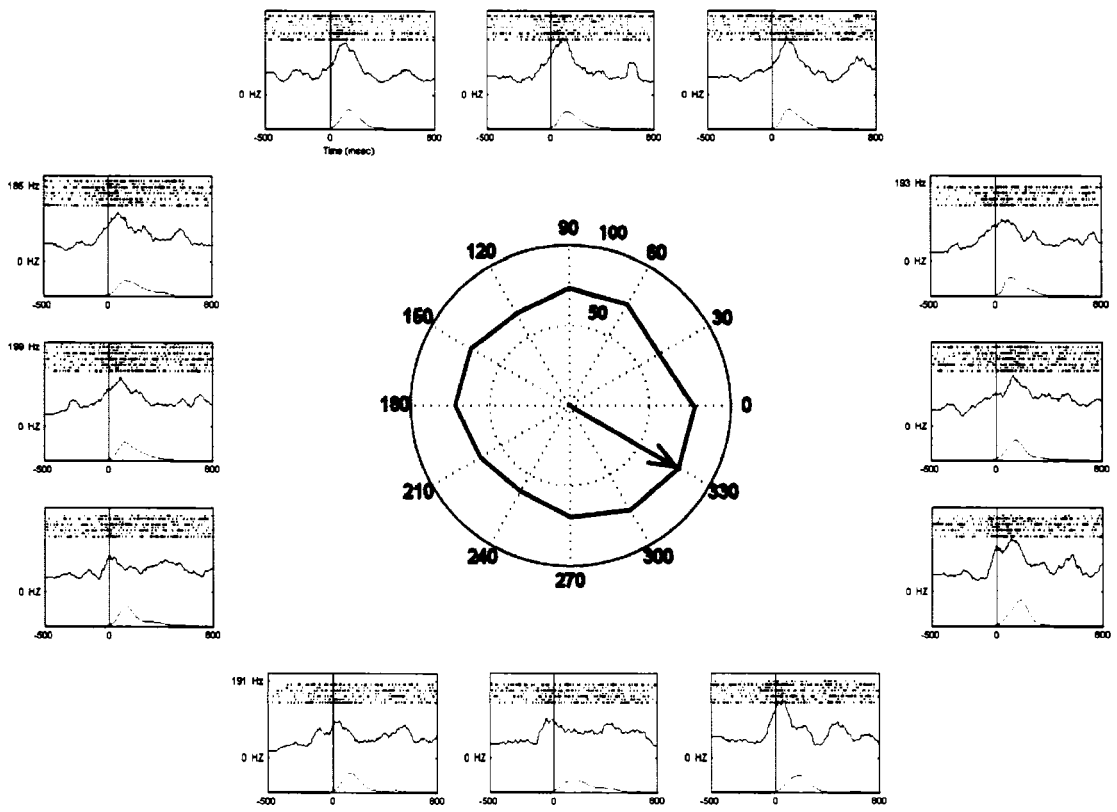


Figure 3.1.4. CT set, thalamic neuron **B**.

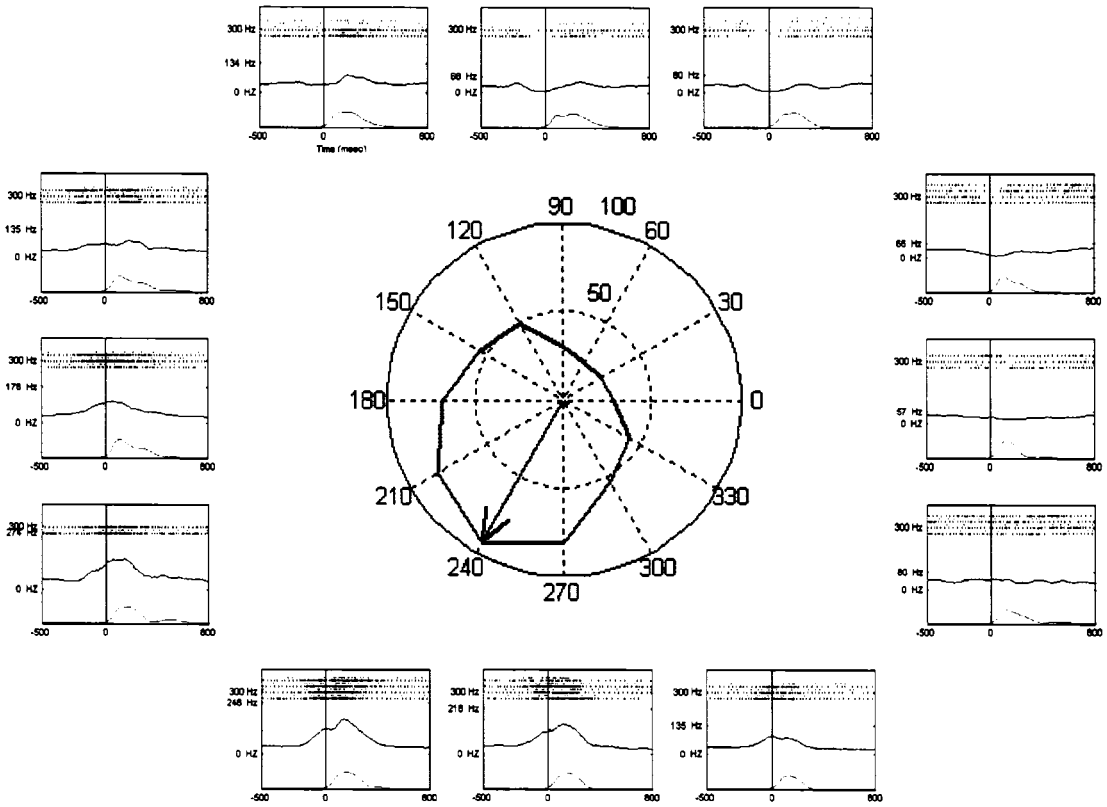


Figure 3.2.1. Neural activity of cortical neuron **A** from a potential TC set. Cortical neurons included in TC sets were orthodromically activated by thalamic stimulation, and thalamic neurons in the same TC set were located within 50 μm of the thalamic stimulation site from which the orthodromic activation was elicited. Figure details same as Figure 3.1.

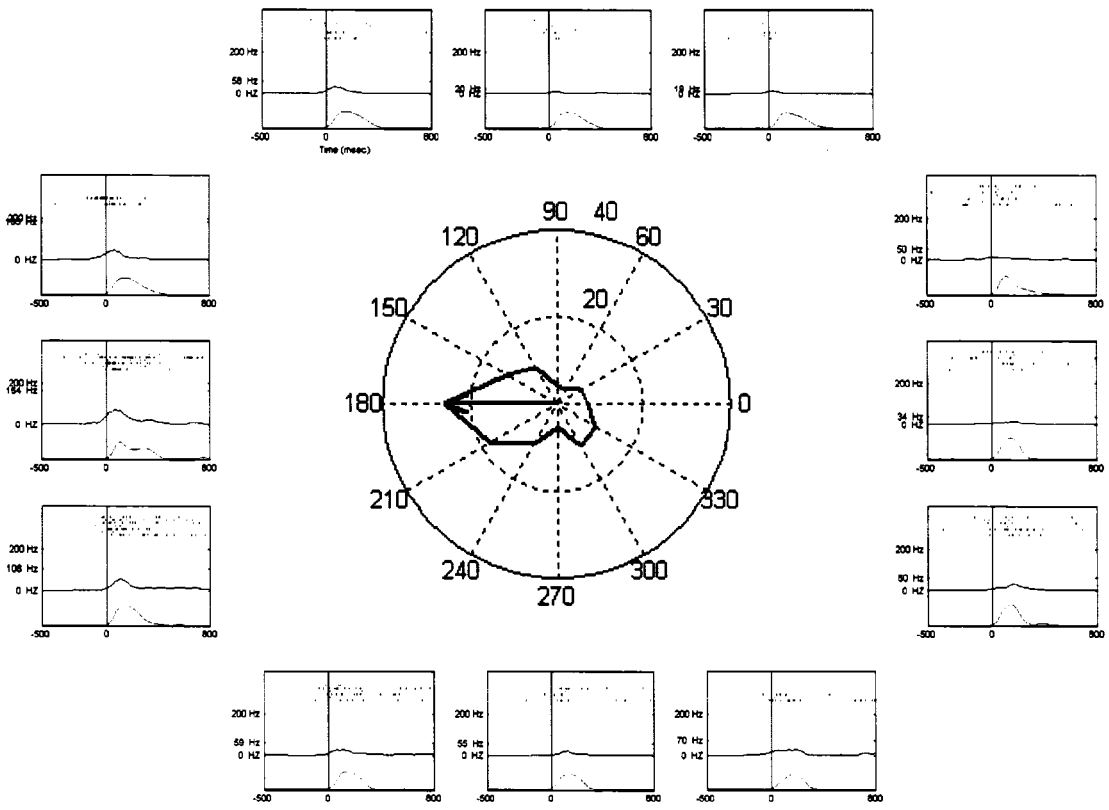


Figure 3.2.2. TC set, cortical neuron **B.**

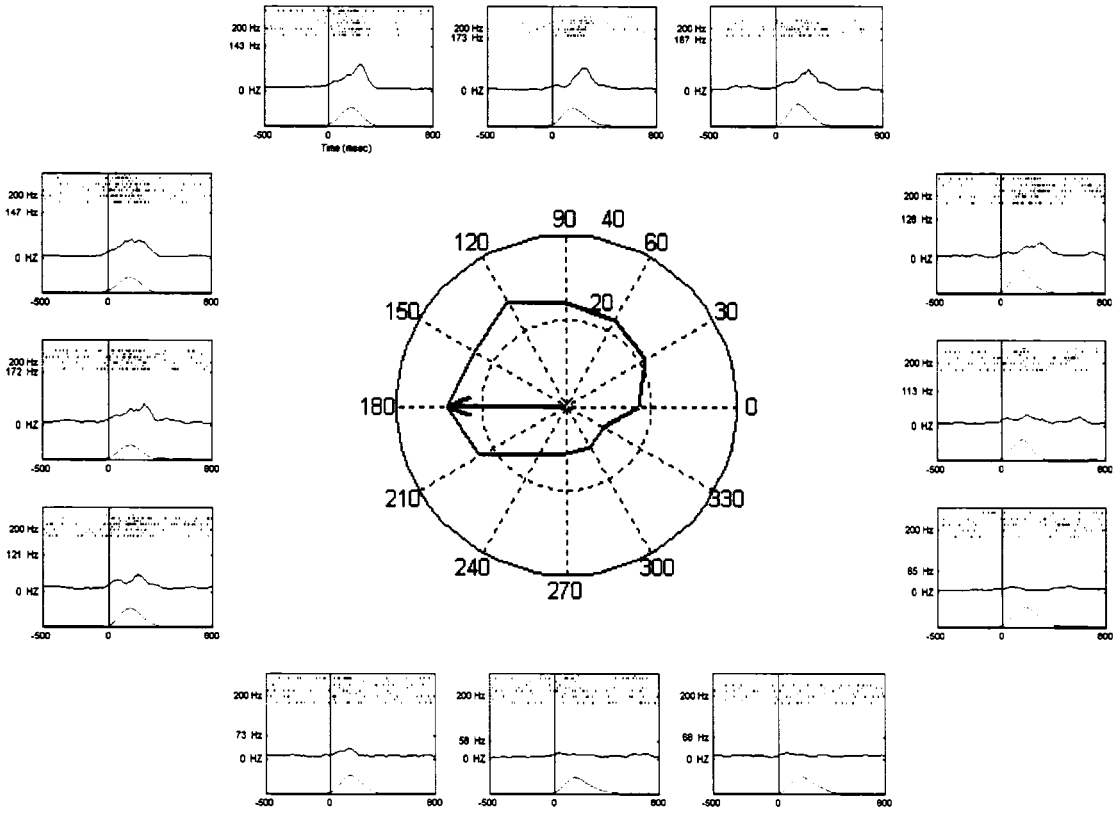


Figure 3.2.3. TC set, thalamic neuron **A.**

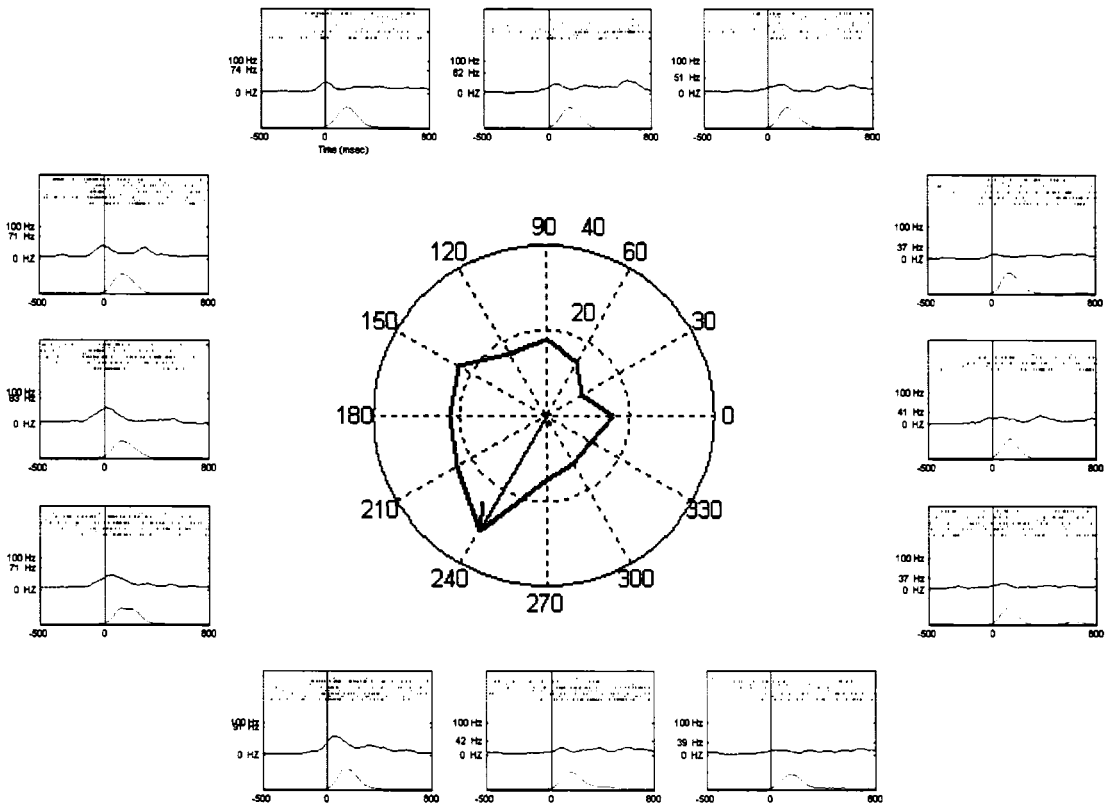


Figure 3.2.4. TC set, thalamic neuron **B**.

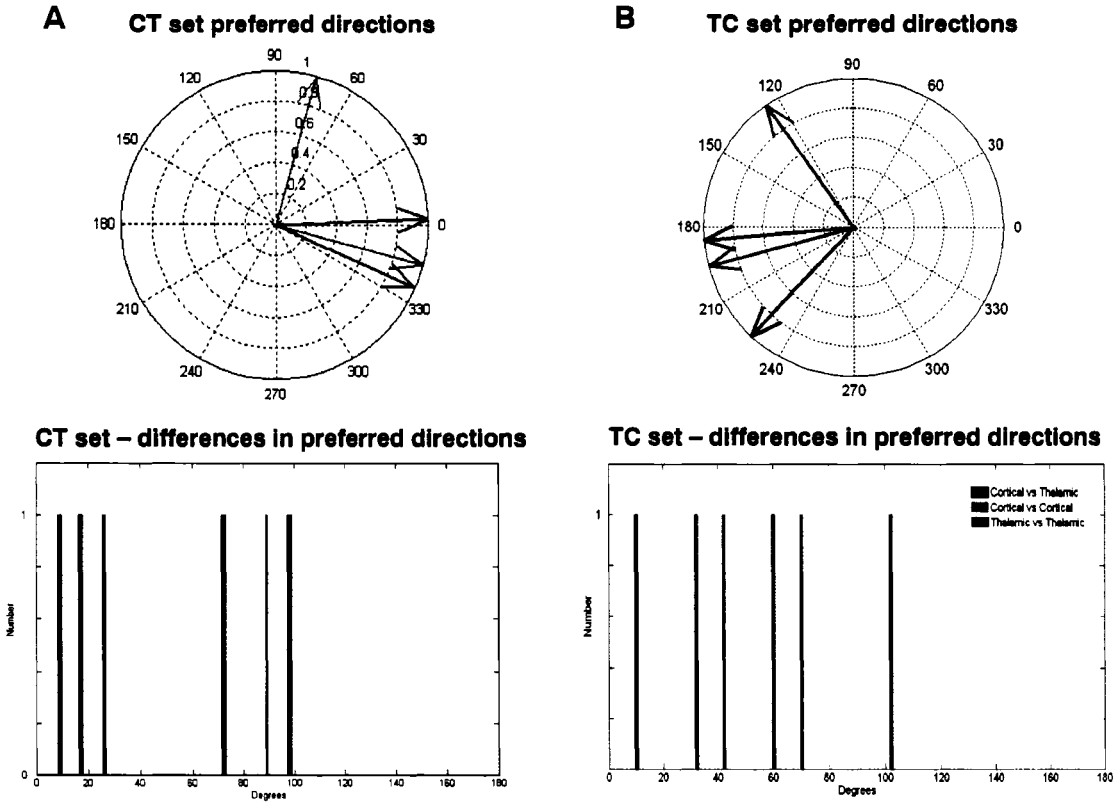
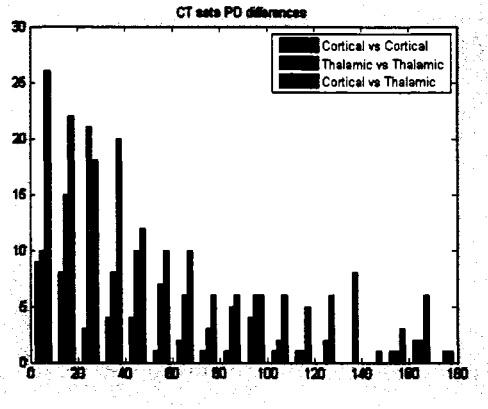


Figure 3.3. The preferred directions, derived from the von Mises fit, for each of the neurons within the CT and TC sets from Figures 3.1 and 3.2 are displayed here. The top portions of each panel show the preferred directions in a polar plot form. Preferred directions of cortical neurons are shown in blue and those of thalamic neurons are shown in red. In the lower panels the differences between the preferred directions of the neurons in a potentially connected set are displayed. Similar preferred directions are indicated as small degree differences and fall to the left side of the graph. **A**, CT set preferred directions and differences. **B**, TC set preferred directions and differences.

A



B

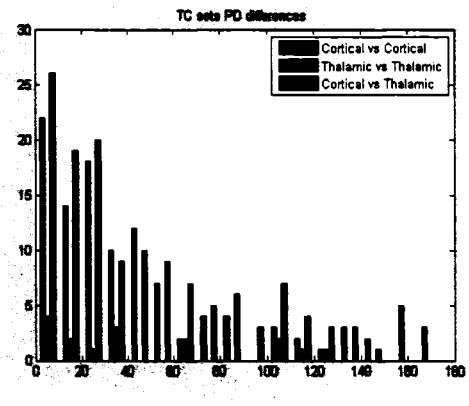


Figure 3.4. The differences in preferred directions within potential sets are pooled to provide a population based measure of dispersion of preferred directions. **A**, Shows the pooled differences in preferred directions from all CT sets. Colored bars represent differences grouped by neuron type: blue bars represent differences between cortical neurons, green bars between thalamic neurons and red bars show differences between a cortical and thalamic neuron. The distribution is heavily skewed towards small differences for each category. (t-test, $p<0.01$). **B,** Pooled differences for TC sets. Cortical-cortical and cortical-thalamic differences are significantly biased towards small differences (t-test, $p<0.01$). The thalamic-thalamic differences show a trend towards small differences (t-test, $p=0.18$).

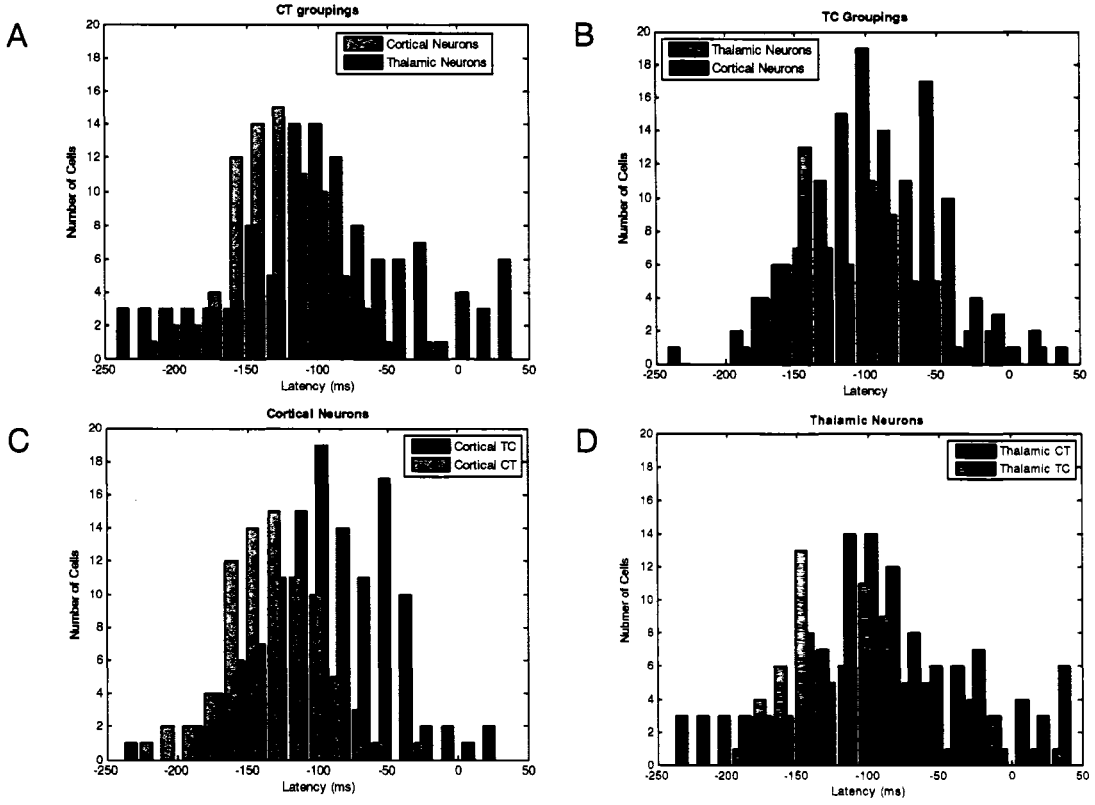


Figure 3.5. Histograms of latency to onset of neural activity relative to the onset of movement towards the preferred target are shown. Negative latencies indicate that modulation preceded the onset of movement. **A**, Latency of cortical neurons (blue) and thalamic neurons (red) associated with CT groups. Cortical neurons show a significant longer onset latency (-120 ms ± 23 ms) than thalamic neurons (-95 ms ± 46 ms) (ANOVA, $p<0.01$). **B**, The latencies of cortical and thalamic neurons did not differ within TC groups. **C**, When comparing different categorizations of cortical neurons (CT vs. TC), the cortical neurons associated with CT groups showed longer latencies than those in TC groups (-120ms vs. -96ms, ANOVA, $p < 0.01$). **D**, Thalamic neurons showed no differences across categories.

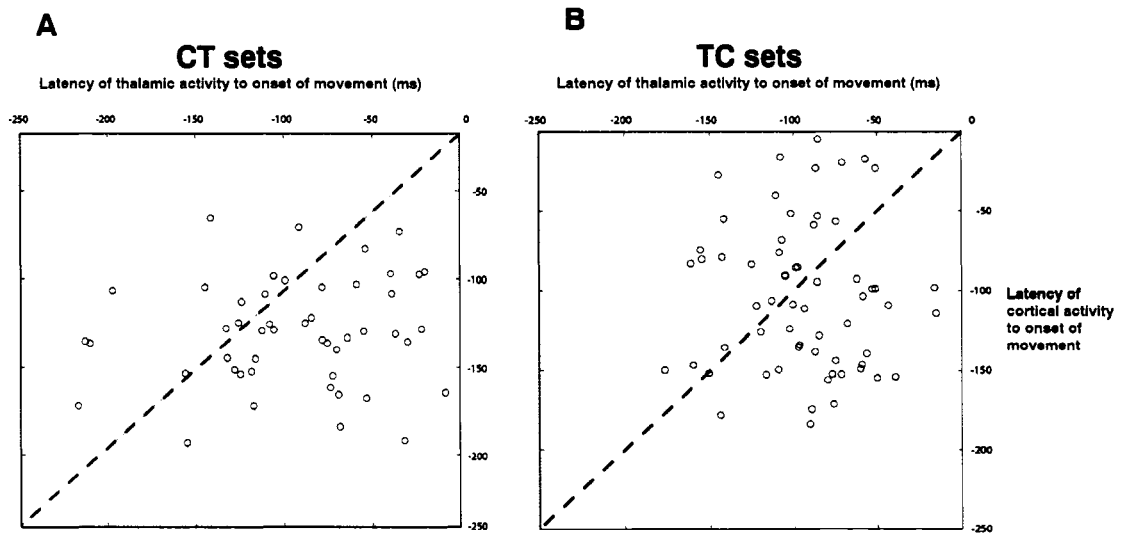


Figure 3.6. The mean onset latencies of thalamic vs. cortical neural activity relative to the onset of movement towards the target closest to the mean preferred direction of the set is shown in these scatter plots. Each data point represents a single set. The dashed line indicates equal thalamic and cortical latencies. Points that fall below the line signify a longer mean cortical than thalamic latency. In those sets, the cortical neurons had a tendency to fire earlier in the task than the thalamic neurons. **A**, The CT sets show a small, but significant tendency ($p<0.05$) to fall below the dashed line, indicating that within individual sets, there is a tendency for cortical neurons to modulate their activity earlier than thalamic neurons during this task. **B**, The latencies within TC sets show no clear relationship.

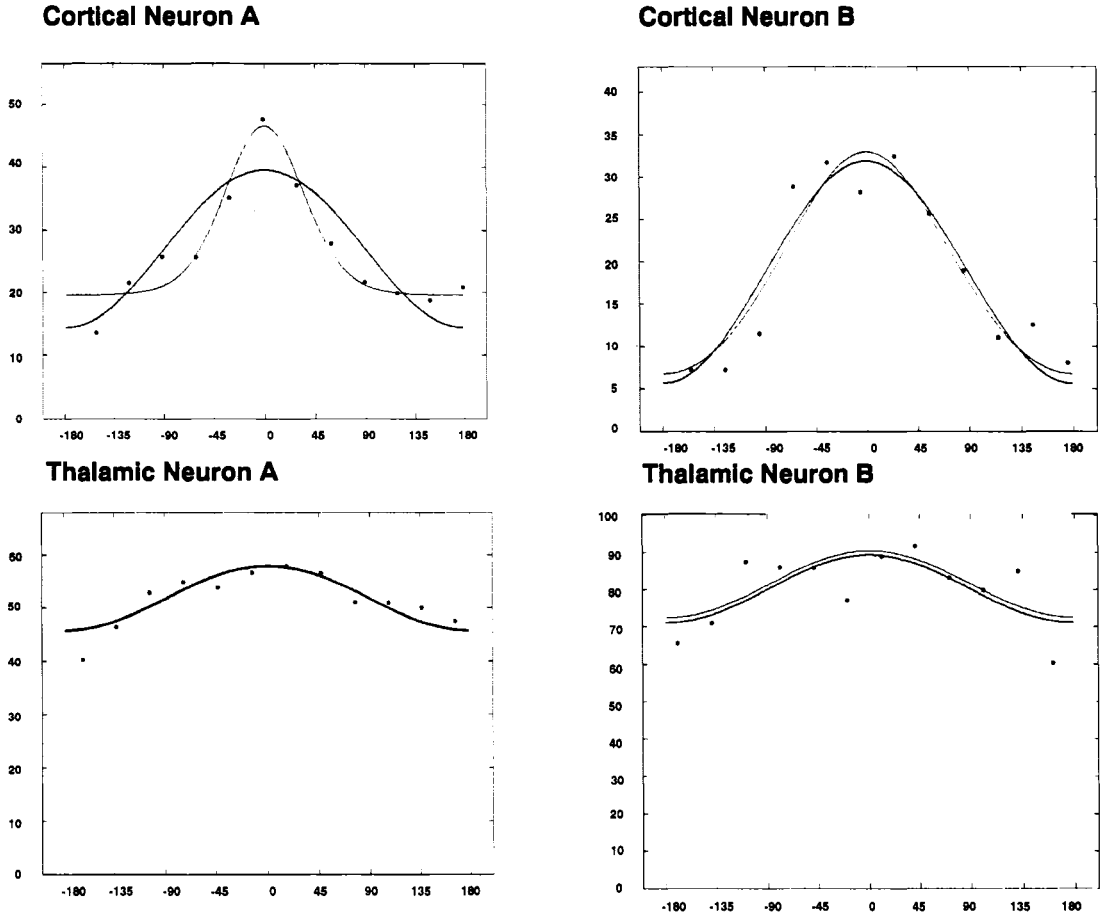


Figure 3.7. The directional tuning curves, based on the von Mises function (red) and the cosine function (blue) for the neurons in the CT set from Figure 3.1 are shown above. Cosine tuning curves are shown for comparison. Both cortical neurons (A and B) show sharper tuning (σ: A = 41.5°, B = 79.5°) than the potentially connected thalamic neurons (σ = 90° for each).

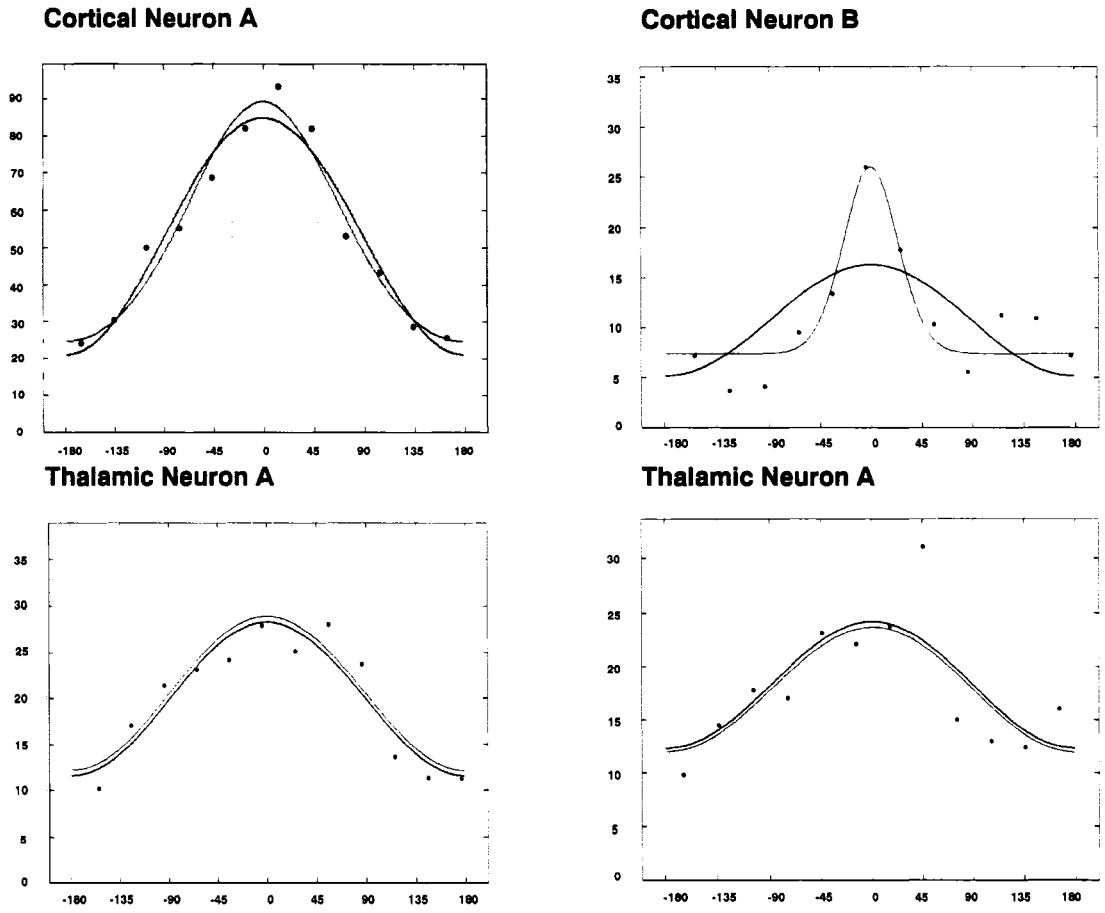


Figure 3.8. The directional tuning curves for the neurons in the TC set from Figure 3.2 are shown above. Details are the same as Figure 3.7. Both cortical neurons (A and B) show sharper tuning (σ: A = 75.5°, B = 28.5°) than the potentially connected thalamic neurons (σ = 90° for each).

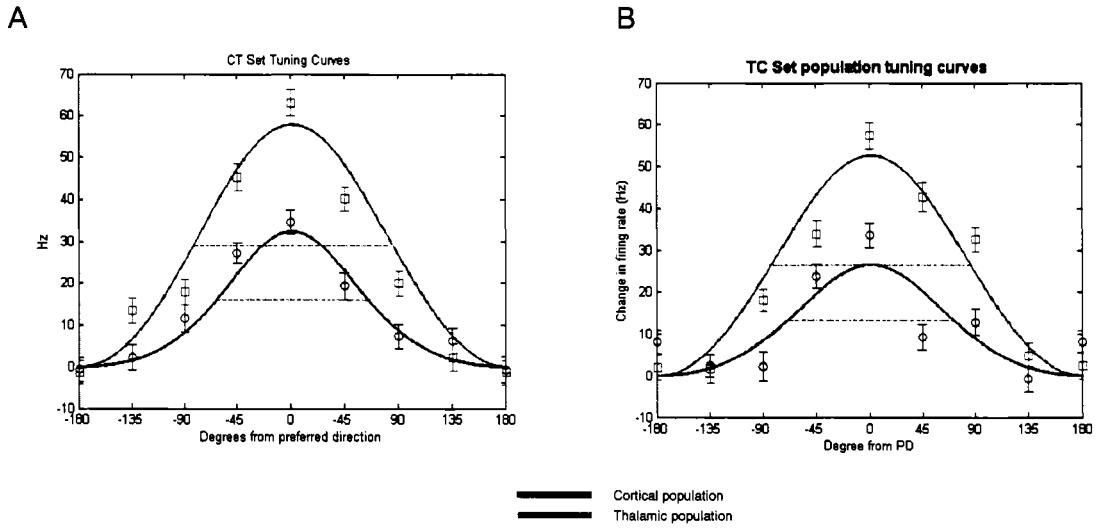


Figure 3.9. The population tuning curves for CT sets and TC sets. Only tuning curves derived from von Mises functions are shown here. **A**, tuning curves from the CT population show that the CT cortical neurons have a mean half width (σ) of 64° and exhibit a mean change in firing rate of 32 Hz when the animal reached towards the preferred target direction. The CT thalamic population tuning curve has a half width (σ) of 84° exhibits a mean peak change in firing rate of 58 Hz. The differences in half widths and depth of modulation are significant (ANOVAs, $p < 0.001$). **B**, TC cortical neurons had a half width (σ) of 71° and a mean peak change in firing rate of 26 Hz, while the TC thalamic neurons had a half width (σ) of 86° and a mean peak change in firing rate of 52 Hz. The differences in half widths and depth of firing were both significant (ANOVAs, $p < 0.001$).

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Chapter IV

Discussion

The present studies confirm that the arm area of the primary motor cortex in the monkey contains two classes of neurons that can be antidromically activated from the thalamus and are presumed corticothalamic (CT) neurons. As in the cat and rabbit, these have properties that correspond to the neurons that, in anatomical studies, originate in cortical layers V and VI. A substantial body of work has investigated the role of the corticothalamic projection in sleep/wake transitions, synchronization of oscillatory activity, switching response modes or altering receptive field properties of thalamic relay neurons in auditory, somatosensory and visual systems (Steriade, 2001; Steriade et al., 2001; Sherman and Guillery, 2002; Sillito and Jones, 2002; Suga et al., 2002; Worgotter et al., 2002; Steriade and Timofeev, 2003; Li and Ebner, 2007). These proposed functions are well generalized by Sherman and Guillery's model (Sherman and Guillery, 1998) in which layer V corticothalamic neurons act as 'drivers' and layer VI neurons act as 'modulators' of thalamic activity. However, these studies have primarily utilized slice or anesthetized preparations, and since the corticothalamic projection is both dependent on and may help regulate behavioral states, it is important to investigate the corticothalamic projection in awake, behaving subjects. We discuss

here how our results from the motor cortex and thalamus of awake performing monkeys, contribute to these existing models of corticothalamic function.

Basic characteristics of "active" vs. "inactive" CT neurons.

The primary distinguishing feature between the two populations of CT neurons that we identified was the presence or absence of spontaneous or task-related activity during an experimental recording session. The two CT populations differed based on several other features as well. The 'active' corticothalamic neurons had shorter conduction latencies and lower thresholds to stimulation and were located more superficially in cortex than the 'inactive' corticothalamic neurons. Based on other detailed neuroanatomical and electrophysiological studies, we presumed that the active and inactive cells were layer V and VI corticothalamic neurons, respectively.

Layer VI corticothalamic projection.

The finding that the presumed layer VI corticothalamic neurons were virtually silent throughout performance of the task is consistent with others' observations on the activity of layer VI corticothalamic neurons. Beloozerova has shown that layer VI neurons in rabbit and cat exhibit very low rates of spontaneous activity during locomotion and balancing (Beloozerova et al., 2003a; Beloozerova et al., 2003b; Sirota

et al., 2005), although, in the cat, they did find a subpopulation of moderately conducting layer VI neurons with low firing rates during step-related behavior (Sirota et al., 2005). In unpublished data, the authors have continuously recorded the neural activity of unrestrained rabbits over a 48 hour period, and they continue to find very low rates of spontaneous activity in layer VI corticothalamic neurons, even across the sleep/wake cycle (personal communication). It remained to be seen, however, whether these cells might be active at some time during a visually-guided reaching task, as opposed to locomotion, which might be generated from spinal levels. They were not. Instead, the "inactive" neurons were only detected by the antidromically conducted spikes that were evoked by stimulation in the thalamus.

During our recording sessions, we attempted to activate some silent corticothalamic neurons by presenting the monkey with a variety of different stimuli, outside the context of the behavioral task. These included numerous visual stimuli, such as pictures of monkeys of both genders with a variety of postures and facial expressions, predators and natural landscape settings. We gave the monkey opportunities to choose from a variety of appetitive rewards (apple, apricot, banana or strawberry), and we forced the monkey to use fine dextrous movement to pick food rewards from a Kluver board. At times we allowed the monkey to behave freely (with head restrained), and at other times, we allowed the monkey to fall asleep during the recording session. Despite presenting stimuli that should elicit a range of emotional,

motor and arousal state responses, we were never able to drive action potentials in the layer VI corticothalamic projection.

While we did not identify a stimulus to drive the layer VI corticothalamic neurons and their presence was only detected by the antidromically conducted spikes that were evoked by stimulation in the thalamus, the size and nature of the projection suggests an important functional role that remains to be elucidated. At present, we can only hypothesize on that role.

There is a relatively broad hypothesis that the layer VI corticothalamic projection plays a role as a modulator of thalamic activity. Sherman and Guillery define modulators as inputs that can alter the effectiveness of a driving input, without contributing significantly to the general pattern of the message (Sherman and Guillery, 1998). An important modulatory effect is the switch between burst and tonic modes in thalamic relay neurons. When in burst mode, a thalamic neuron is highly sensitive to the presence of a stimulus and will respond with an all-or-nothing burst response. Compared with burst mode, a neuron in tonic mode responds in proportion to the strength of a stimulus, but with an overall higher detection threshold (Sherman, 2001). It has been shown that activity of some of the modulatory inputs to the thalamus can switch thalamic neurons between bursting and tonic response modes. For example, application of ACh in vitro, normally released by brainstem afferents from the

parabrachial region or the pedunculopontine tegmental nucleus, eliminates low threshold Ca^{+} spikes and switches cells into tonic mode (Bickford et al., 1993; Lu et al., 1993). There is also evidence that application of metabotropic glutamate agonists, which mimic some corticothalamic action, cause thalamic neurons to switch from burst to tonic mode (Guido and Weyand, 1995; Godwin et al., 1996)

The axonal terminals of layer VI CT neurons are well suited to be modulators of burst/tonic response mode switching. Studies in the motor system show that layer VI neurons terminate with small boutons at distal dendrites onto both ionotropic and metabotropic receptors (Kakei et al., 2001; Li et al., 2003; Reichova and Sherman, 2004; Zhang and Jones, 2004), and that they branch to innervate cells in the thalamic reticular nucleus. The response mode of a cell is dependent on the inactivation or de-inactivation of I_T, which requires the maintenance of depolarization or hyperpolarization of ~100 ms. When the I_T current is de-inactivated, a cell responds in burst mode, and when inactivated, it will respond in tonic mode. The layer VI small boutons at distal dendrites are appropriately placed to depolarize dendrites and drive them towards the depolarized state required for burst responses. Activation of the metabotropic receptors produces a slow (>10ms), but long lasting response, often with a duration of hundreds of ms or more, that is ideal for maintaining a depolarized, or hyperpolarized state required for switching response modes. Activation of cortical and brainstem inputs to thalamic relay cells can elicit sustained EPSPs to inactivate I_T,

thereby producing tonic firing, whereas local GABAergic inputs could elicit sustained IPSPs and cause the opposite result.

In our lab we have witnessed this transition between bursting and response tonic modes in vivo, but we have not correlated these transitions with layer VI activity. It is possible that spontaneous layer VI activity did modulate these transitions, but our ability to record from only one or two cortical neurons at any given time limited our opportunities to capture this activity. If the response mode transitions are very specifically regulated, so that only a tiny percentage of thalamic neurons make a transition under appropriate situations, then it would be very unlikely for us to witness the layer VI activity unless we replicate those highly specific circumstances. In a recent study Li and Ebner (Li and Ebner, 2007) showed that activation of layer VI neurons by microstimulation can sharpen and/or rotate the angular tuning curves of single thalamic neurons in VPM of an anesthetized rats. This effect was only seen when stimulation occurred in 'matched' barrel columns of cortex. The very high specificity of the effect of stimulation witnessed in their study supports the possibility that layer VI corticothalamic neurons are generally quiet and show activity only in very highly specific situations.

It is also possible that modulation within the motor system might be more prevalent with complex or sequential movements, fine movements of the distal musculature, internally or memory guided movement, or novel or unlearned movements. Since our study utilized visually guided, overlearned, simple movements

using the proximal muscles, we might not have uncovered the correct situation to reveal corticothalamic layer VI activity.

Layer V corticothalamic projection

Presumed layer V corticothalamic neurons were active during the resting state, and their activity changed during a reaching task. We investigated this activity further, as well as the characteristics of cortical activity evoked synaptically at short latencies by stimulation in the cerebellar-receiving region of the motor thalamus.

In order to maximize the probability that the cortical and thalamic neurons studied were actually connected, cortical neurons were grouped into sets with thalamic neurons based on their responses to thalamic stimulation. Those that exhibited antidromic responses to thalamic stimulation were assigned to CT sets and were presumed to originate in cortical layer V. All antidromically activated cortical neurons that responded to stimulation from one thalamic site were assigned to the same CT group, along with all the thalamic neurons that were located within a short distance from the tip of the stimulation electrodes and potentially received synaptic input from cortical neurons in that set. Orthodromically activated cortical neurons were grouped in a similar fashion into TC sets. While the origin of TC cortical neurons could not be shown definitively, based on their cortical depth it was presumed that many reside in

the more superficial cortical layers (layer I-III). In addition to the antidromic and orthodromic responses to thalamic stimulation, the low dispersion of preferred directions provided evidence for potential connectivity within sets. All classifications of sets (CT and TC) showed a limited range of preferred directions.

Cortical neurons in both CT and TC sets exhibited more sharply tuned directional responses than did thalamic neurons. The wider tuning of thalamic neurons in the cerebellar receiving region is consistent with the broad tuning curves described by others for cerebellar neurons (Fortier et al., 1993). This implies that it is cortical processing that limits the spatially-directed action of cortical efferents, and not the input to the cortex from the thalamus.

Within the CT sets, all cortical neurons began to modulate their activity prior the onset of movement to a preferred target, and their activity was modulated earlier,with respect to movement, than was that of thalamic neurons. This was true when cortical and thalamic neurons within a set were compared, as well as for the populations of corticothalamic and thalamic cells studied. This potentially places the cerebellar-receiving thalamus in more of a feedback role, or at least the role of modulating an ongoing cortical signal to elicit movement, rather than initiating it.

Cortical neurons within TC sets were not activated as early, with respect to movement, as were CT cortical neurons, and these cortical cells also did not lead the

activity of the thalamic cells in the same set. This difference between TC and CT cortical neurons, together with the difference in depth of the two cortical populations and the fact that our thalamic stimulus conditions did not drive cortical neurons both antidromically and orthodromically suggests that cortical cells in TC sets really are a different group from those that project to the thalamus and are in layers II and III of the motor cortex.

Our results are consistent with other findings that layer V corticothalamic neurons were active during simple and complex locomotion and during postural correction in the rabbit (Swadlow, 1994; Beloozerova et al., 2003a; Beloozerova et al., 2003b; Beloozerova et al., 2003c). The presence of corticothalamic activity that is potentially an efferent copy of patterned motor output to the spinal cord emphasizes the role of the cortex in locomotion, as well as in visually-guided reaching. This is true even though locomotion can be elicited by unpatterned stimulation of the midbrain locomotor region in a decerebrate animal, without the benefit of a patterned signal from the motor cortex (Mori et al., 1978).

Sherman and Guillery have proposed that the thalamus plays a major role as a monitor of motor output, and that the corticothalamic projection is an essential component of this system. They base their hypothesis on a growing body of anatomical evidence that demonstrates that virtually all driving afferents to the thalamus are

branches of projections to other centers in the brainstem or spinal cord that relate directly, or indirectly to motor functions.

In the visual system, retinal ganglion cells innervate the thalamic lateral geniculate nucleus, which then projects mainly to the primary visual cortex. However, many retinal ganglion cells also send axons to other centers, including the superior colliculus and the pretectum. There is evidence that many of these axons are branches of axons that go to the LGN (Bunt et al., 1975; Vaney et al., 1981; Linden and Perry, 1983; Jhaveri et al., 1991; Sommer and Wurtz, 2002), and one study in hamsters even reports that all retinal ganglion cells project to the superior colliculus (Chalupa and Thompson, 1980). It remains possible that all inputs to LGN are branches of axons that project to midbrain or brainstem, and as studies are performed using better techniques, more evidence has accumulated supporting this possibility (Tamamaki et al., 1995). These patterns may also generalize to other 'first-order' thalamic nuclei. For example, the pathways to the ventral posterior nucleus of the thalamus, concerned with ascending somatosensory information, receives major projections from medullary nuclei that are innervated by axons that also have spinal branches relating to the segmental reflexes of the spinal cord (Brown and Fyffe, 1981).

There has been evidence available for some time showing that there are driving afferents from the cortex to so-called higher-order thalamic nuclei and that these axons are often branches of neurons projecting to the brain stem. Several studies have shown

that axons from the motor, somatosensory or visual cortex that terminate in the thalamus are branches of long descending axons that go to or through the brainstem, particularly to tectum and the pons (Casanova, 1993; Deschenes et al., 1994; Bourassa and Deschenes, 1995; Bourassa et al., 1995; Veinante et al., 2000).

Cerebellar receiving thalamus differs however from first and higher-order thalamic nuclei in that it receives potential driving inputs from two sources, the layer V corticothalamic and the cerebellothalamic projections. One intracellular recording study showed that thalamic relay neurons exhibited remarkably similar synaptic activation properties from cerebellar and cortical afferents (Sawyer et al., 1994), As described above, branches of corticofugal axons from motor cortex reach cerebellar receiving areas of the thalamus. Axons from the deep cerebellar nuclei, particularly the dentate, send projections to the thalamus and also to the pontine reticular formation and the red nucleus (Stanton, 1980, 2001). Shinoda showed that axons of dentate and interpositus that projected to thalamus gave off collaterals to the red nucleus and made contacts with rubrospinal neurons (Shinoda et al., 1988). The strength of the cerebellothalamic projection has been well established as a strong, excitatory pathway from cerebellum to M1, so there is little doubt about its role as a driver of thalamic activity (Allen and Tsukahara, 1974; Na et al., 1997; Hoover and Strick, 1999; Holdefer et al., 2000). The role of the layer V corticothalamic projection however, remains in doubt.

In our studies, we were able group cortical and thalamic neurons into potentially connected groups, which provided us with a unique opportunity to assess the potential influences of corticothalamic and thalamocortical projections on their targets. Our results show that the layer V corticothalamic projection to cerebellar receiving motor thalamus does carry a signal that may be an efferent copy of the output of M1 that is sharply tuned with respect to movement direction and is modulated prior to the onset of movement. The thalamic neurons that presumably receive this input show modulation later and are more broadly tuned than these cortical neurons. The latency data show that the CT cortical neurons modulate their activity ~25 ms earlier than the potentially connected thalamic neurons, which is a large difference to support a direct monosynaptic influence on the thalamic neurons via the more rapid corticothalamic neurons from layer V.

There remain many ways that the motor-related activity of the layer V corticothalamic projection may influence thalamic activity. Some current models propose that the cerebello-thalamo-cortical projection is related to movement duration (Ivanusic et al., 2005), and that changes in cerebellar thalamic activity might influence the duration or timing of motor cortical neurons (Meyer-Lohmann et al., 1977; Hore and Flament, 1988). In the context of these models, the layer V corticothalamic projection, carrying an efferent copy of current M1 output, could be an appropriate gatekeeper for ascending cerebellar information related to the duration or coordination of an action. In this role, the modulation of activity of the layer V corticothalamic

neurons would not drive the activity of thalamic neurons, but instead would serve to regulate the passage of cerebellar information destined for the cortex, perhaps by acting primarily though inhibitory interneurons.

A further possible role for the layer V corticothalamic projection is that of inducing plasticity at the level of the thalamic synapse. Aumann and Horne (Aumann and Horne, 1999) have shown that after adaptation to a novel load, rats showed an increase in the number of docked vesicles at cerebellothalamic dendritic zones. In a subsequent study, Aumann et al., showed that rat cerebellothalamic synapses are capable of expressing LTP *in vitro* (Aumann et al., 2000). In an *in vivo* situation, the layer V corticothalamic projection could provide the neural input necessary to induce the longer-term ultrastructural changes or the short term LTP witnessed in these studies. In this role, the layer V corticothalamic projection may actually be acting as a modulator, working to strengthen or weaken synapses throughout the thalamus

The demonstration that a potential efferent copy of the motor output of M1 goes to thalamus has importance for understanding the role of the thalamus and the role of the cerebellum and its contribution to motor control. Our results are consistent with the proposal by Sherman and Guillery that thalamus receives a monitor of motor output, but how the 'driver like' afferents from both cortex and cerebellum interact remains to be determined.

Conclusion

The work contained in this thesis addresses the characteristics and role of the corticothalamic projections in the motor system of the awake, performing primate. They represent the first studies to record from cortical neurons identified by antidromic activation from the thalamus in the primate, and also the first attempt to record from functionally related groups of cortical and thalamic neurons. The finding that the layer VI corticothalamic projection is virtually silent confirms similar findings from other studies and expands those results to include neurons studied during reaching movement of primates. Identifying the layer V corticothalamic projection as carrying what could be an efferent copy of the output of M1 is an electrophysiological confirmation of a prediction from anatomical data. Our analysis of the functional interaction between cortex and thalamus suggests that the Layer V corticothalamic projection may be one of the drivers of thalamic activity together with the cerebellothalamic projection, but it may also have more modulatory influences on thalamic activity.

Notes to Chapter IV

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VITA

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