Exp Brain Res (1992) 88:140–150

Experimental Brain Research



# Cortical modulation of thalamo-cortical neurons relaying exteroceptive information: a microstimulation study in the guinea pig

**C. Rapisarda[1], A. Palmeri[2], and S. Sapienza[2]**

[1] Cattedra di Fisiologia Generale, Istituto di Fisiologia Umana, Università di Bologna, Piazza di Porta S. Donato 2, I–40127 Bologna, Italy
[2] Istituto di Fisiologia Umana, Università di Catania, Viale Andrea Doria 6, I–95125 Catania, Italy

Received July 26, 1990 / Accepted July 18, 1991

**Summary.** The nature and organization of cortical influences on somatosensory thalamic neurons were investigated in the guinea pig in order to ascertain if mechanisms subserving sensory-motor integration in the thalamus are as precise as has previously been demonstrated in the agranular frontal cortex (AGr) and granular parietal cortex (Gr). The study was carried out on 14 chronically-implanted awake animals. In each experiment one or two motor foci within AGr and Gr were identified according to the region of the movement evoked by intracortical microstimulation at the lowest threshold stimulation (usually 5–15 μA). Spontaneous activity of 182 thalamo-cortical single neurons was recorded in the nucleus ventralis thalami (VT). The neurons were also identified by their response to activation of cutaneous receptive fields (RFs) located in regions of vibrissae or limbs, and then tested for cortical stimulation with a pulse intensity equal to the threshold for evoking motor effects. During the cortico-thalamic tests, the duration of stimulating trains was reduced in order to avoid the appearance of limb or vibrissa movements which could activate somatosensory ascending pathways forwarding peripheral messages to VT. The cortical control on VT neurons appears to be organized in a very precise manner. It was seen that: 1) The influences on these neurons relaying exteroceptive signals specifically emanated from AGr and Gr areas which in turn received exteroceptive input. 2) The vibrissa units responded to stimulation of foci in either AGr or Gr but the reactivity was greater upon stimulation of Gr than AGr. The incidence of responses was very high when the vibrissa RF was overlapping or adjacent to the region of the cortically-evoked vibrissa movement. The response pattern was mostly excitatory. Responses were rarely observed when vibrissa RF lay distant from the vibrissa moved by cortical stimulation. 3) Neurons with limb RFs responded constantly to stimulation of Gr foci only when the RF was overlapping or adjacent to the region of the cortical motor target; in these two conditions the response pattern was excitatory and inhibitory, respectively. Inhibitions only concerned neurons with forelimb RFs. Responses to stimulation of AGr were rarely obtained. From a functional point of view, the excitatory nature of the cortical control on thalamo-cortical VT neurons suggests that a cortical signal inducing movement of a given body part is able to enhance the afferent transmission of somatosensory messages arising in the same body part. Concerning the control on forelimb neurons, this enhancement would be further amplified by a sort of "descending" surround inhibition which impairs transmission of messages coming by adjacent body parts.

**Key words:** Ventral thalamic nucleus – Cerebral cortex – Sensory modulation – Guinea pig

*Offprint requests to:* C. Rapisarda

## Introduction

This study is a part of a research line investigating phenomena of sensory-motor integration at different levels of the somatosensory afferent pathway in the guinea pig. As a first step, it was demonstrated that at the cortical level, analogously to other mammals, a spatial correspondence exists between sensory input and motor output in the three body representation areas which were identified in the agranular frontal cortex (AGr) and granular parietal cortex (Gr); the receptive field (RF) of a given cortical neuron and the movement evoked by stimulation of the same recording site were usually confined to the same body region (Rapisarda et al. 1990).

The aim of the present work was to extend the investigation in order to determine if in the guinea pig, thalamic mechanisms of sensory-motor integration are as precise as those found at cortical level. In our experiments we used chronically-implanted preparations to test

single exteroceptive thalamo-cortical (TCR) neurons of nucleus ventralis thalami (VT: including the nucleus ventralis posteromedialis, VPM, and the nucleus ventralis posterolateralis, VPL) for intracortical microstimulation (ICMS) of foci which evoked vibrissa or limb movements at the lowest threshold. It was possible to demonstrate that an early facilitation specifically occurs on thalamic neurons whose RF overlapped the cortical motor target. Functionally, it could mean that a corticofugal motor command inducing movement of a restricted body region would enhance the corticopetal transmission of exteroceptive messages coming from the region controlled by the cortex. Preliminary reports have been published in abstract form (Rapisarda et al. 1986a, b, 1987a, b, 1988).

## Methods

Fourteen guinea pigs (*Cavia porcellus*) weighing 510–550 g were used. The animals were chronically implanted under Nembutal anaesthesia (30 mg/kg, i.p.). Two metallic tubes were fixed onto the skull surface by acrylic resin and stainless steel screws in order to fix the head painlessly to the stereotaxic frame. A Plexiglas well (20 × 20 mm) was cemented onto the bone above the cortical regions to be stimulated. The wounds were closed and the animals were placed in a hammock and adapted for head restraint usually 1–3 h at a time. Animals showed no discomfort and 3 days after surgery they were ready for experimental sessions. During each session the animals periodically took sweet liquid or pellets; electroencephalographic recordings showed a state of quiet wakefulness also during pheripheral stimulations; the heart rate remained within physiological ranges.

Glass micropipettes (2–4 MΩ) filled with a 3 M NaCl solution were used for ICMS. In each experimental session, one or two micropipettes were stereotaxically positioned onto the cortical surface through small holes in the skull bone. The site of each microelectrode penetration was observed by a dissecting microscope in order to avoid blood vessels. After piercing the dura mater covering vibrissa or limb areas in the lateral part of AGr (AGrl) or in the medial (Grm) or lateral (Grl) part of Gr, one or two microelectrodes were slowly advanced into the deepest cortical layer V to isolate single or pairs of cortical foci evoking movements of single joints or vibrissae at the lowest threshold (cf. Rapisarda et al. 1990). Stimuli were trains of 15 negative-positive pulses (each lasting 200 μs and 100 μs, respectively) at 100–500 Hz. The threshold stimulus intensity for motor effects was usually very low (5–15 μA), never exceeding 20 μA; it corresponded to the current intensity able to evoke a movement on 50% of trials. The threshold values were periodically verified during each experimental session; if they increased above the initial value by more than 50%, the micropipette was removed and another low threshold focus was sought. Motor responses of limbs were usually determined by visual observation of movements and by muscular palpation. In the few cases in which a precise evaluation of lowest threshold for limb movements was not easy, electromyographic recordings were performed by Teflon-coated silver wires inserted in the muscles where cortically-induced twitches were observed. Instead, the evoked vibrissa movements were routinely determined by observation with an operating-microscope.

Extracellular recordings of unitary activity of ipsilateral VT neurons (cf. atlas of Rapisarda and Bacchelli 1977) were carried out by glass micropipettes (7–10 MΩ) filled with a 1 M KCl solution containing pontamine sky blue (4%). The somatosensory properties of each isolated unit were evaluated by examining the discharge changes to natural stimulation. This stimulation was preferred to the electrical one since experiments were performed in awake preparations. Moreover, it is known from previous studies (Harris and Hendrickson 1987) that when the skin is electrically stimulated, sensory thalamic neurons can be activated from larger body parts, ipsilateral and contralateral, than using natural stimuli. Stimulation of cutaneous RFs (a few skin hairs or 1–3 vibrissae) was made by a paintbrush or air jets; deep RFs were identified by pressure with a fine probe, by palpating muscle bellies and passive manipulation of limb joints (Lamour and Jobert 1982; Chapin and Lin 1984; Sievert and Neafsey 1986; Gioanni 1987). Neurons which were not influenced by peripheral stimulation were disregarded. Responsive VT neurons were also identified as TCR units according to their antidromic response to surface cortical stimulation. Stimuli were trains of three pulses (300 μs; 300 Hz) delivered through bipolar silver ball electrodes (interelectrodic distance: 2.0 mm) positioned on the limb or head areas of Gr cortex, according to the lateral (VPL) or the medial (VPM) explored regions of VT. Antidromic responses were recognized for their capability to follow stimulation frequencies higher than 200 Hz, for the constant latency values (variability up to 100 μs) and the positivity of the collision test of antidromic spikes with orthodromic ones evoked by peripheral natural stimulation.

The responsiveness of the TCR VT neurons was then tested for ICMS of the single or pairs of motor cortical foci previously isolated in AGrl and/or Gr. During tests on VT neurons the number of stimulating pulses was reduced to 1–4, but intensity was maintained equal to that for evoking motor effects when 15 shocks were applied. EMG analysis allowed us to verify that no muscular activity was evoked during such cortico-thalamic (CT) tests, so excluding the possibility that the discharges of VT neurons could be influenced by changes of incoming input from the periphery following ICMS. Threshold intensity-train duration relationships showed that 1–4 shocks, with intensity equal to that evoking movement with 15 pulses, were highly ineffective. In fact the intensity needed to elicit movement was significantly higher (2 to 4 times) by using such a short train. Extracellular activity of VT neurons was visualized on a storage oscilloscope and recorded on magnetic tape for computer analysis.

The responses of VT neurons to ICMS were evaluated by converting 60 trials of each CT test into post-stimulus time histograms (PSTHs) and cumulative frequency distributions (CFDs) for bins of 0.1–2 ms. Spontaneous activity was also computed from an equal number of trials in order to evaluate the mean number (+/− standard deviation, S.D.) of spikes in the absence of any intentional stimulation. Excitatory and inhibitory responses were defined as sequences of at least 3 bins with frequency values at more than twice S. D. above or below the mean values during spontaneous activity. The latency of evoked responses was expressed by the time interval from the last effective pulse of the stimulating train to the first bin of the sequence; the duration was measured as the interval between the first and the last bin of the sequence.

The Mann-Whitney test has been used to evaluate the significance of differences between mean values or percentages. The level of significance was set at $P < 0.05$.

In the last 3 experimental sessions of each animal, one or two functionally identified sites along penetrations in VT as well as cortical stimulated sites were marked by iontophoretic deposit of pontamine (10–15 μA cathodic current for 20 min). At the end of observations, the animals were deeply anaesthetized with an overdose of Nembutal and intracardially perfused with saline followed by 10% formaline solution. Histological reconstructions of tracks were made on serial frontal sections stained by neutral red.

## Results

The study was carried out on a total of 182 VT neurons (stereotaxic planes A6.2–A8.2; L1.0–L6.5; V6.5–V9.0) which were identified as TCR units because they generated an antidromic spike following surface cortical

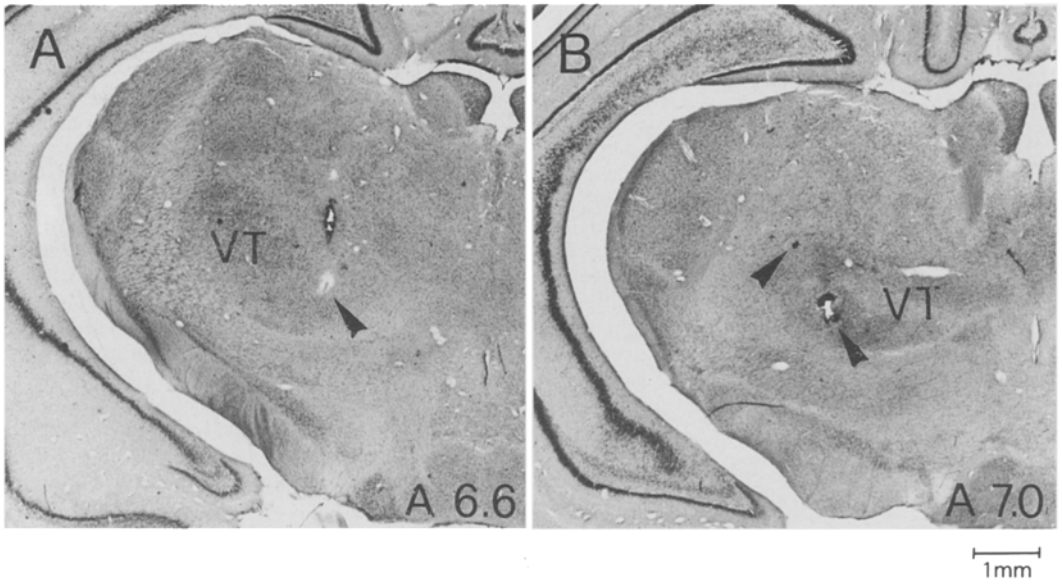



**Fig. 1A, B.** Photomicrographs from two coronal sections of the guinea pig brain through the nucleus ventralis thalami (VT). **A** *arrow* indicates a recorded site in the medial third of VT, in which a neuron was activated by a single vibrissa displacement (see neuron b in Fig. 4). **B** the *two arrows* show two marked sites located in the lateral and middle third of VT, in which a hindlimb neuron and a forelimb neuron (see neuron b in Fig. 6) were recorded, respectively

stimulation (latency: 0.8–3.0 ms). All these neurons were activated by stimulation of contralateral cutaneous RFs with short bursts of 4–5 spikes. A few of these units also responded to deep stimulation, but these responses could be the result of a skin receptor coactivation due to deformation of deep tissues during stimulation. Thus, we have not any evidence of convergence between cutaneous and proprioceptive inputs on VT neurons. Cells giving off unclear responses were disregarded.

Among the studied units, 86 were activated by displacement of 1–3 mystacial or nasal vibrissae and 96 responded to limb stimulation. Out of the limb units, 61 had RFs located in the forelimb and 35 in the hindlimb. Forelimb neurons had small RFs (1–3 $mm^2$ of glabrous or hairy skin) while hindlimb RFs were larger, even covering the entire surface of a limb segment. The spatial distribution within VT of neurons responsive to vibrissa or limb RFs stimulation in the guinea pig recalled the somatotopic arrangement described in rat (Emmers 1987). Vibrissa neurons were located in the medial third of VT. Neurons with forelimb RFs were located in the middle third of the nucleus just medially to those with hindlimb RFs. These hindlimb neurons were preferentially distributed in dorsal and lateral regions of the lateral third of the nucleus (see Fig. 1 for examples).

Motor effects induced by ICMS of vibrissa areas consisted of retraction or adduction of 1–3 vibrissae; elbow flexion, wrist extension, knee flexion or ankle dorsiflexion were most commonly observed following ICMS of limb areas. ICMS with a threshold intensity for eliciting motor effects never evoked antidromic responses of VT units which had been preliminarily recognized as TCR following cortical surface stimulation. The transsynaptic VT responses, excitatory as well as inhibitory, were generally obtained by applying 2–3 shocks, rarely 1 shock alone.

Since no intracellular recordings were made in this study, it was not possible to establish the nature (inhibitory or disfacilitatory) of the phenomena giving rise to

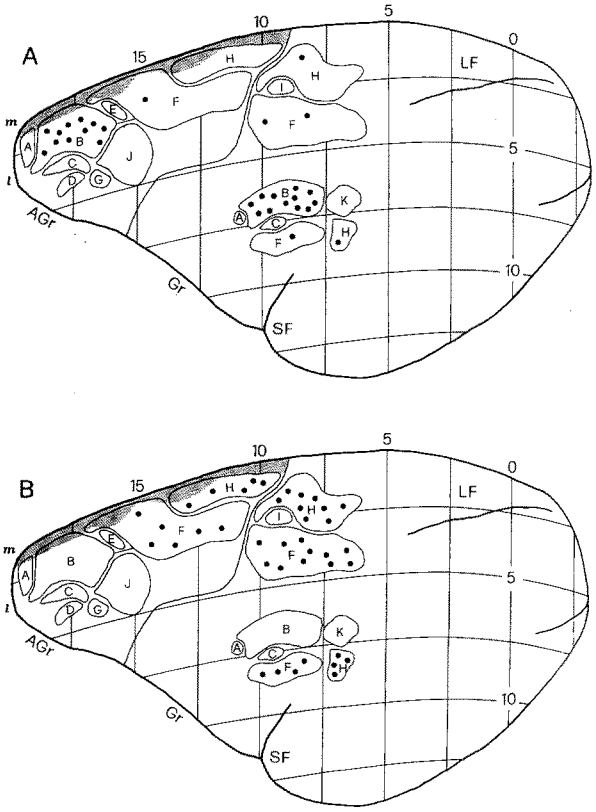



**Fig. 2A, B.** Schematic view of the guinea pig cerebral cortex with a superimposed stereotaxic mm-grid where the various body representations are depicted. Filled circles indicate all the cortical sites which were stimulated during experiments to test VT neurons with vibrissa (panel **A**) and limb (panel **B**) receptive fields. *Abbreviations:* AGr – agranular cortex with its medial (m) and lateral (l) subdivisions; Gr – granular cortex; LF – lateral fissure; SF – sylvian fissure; A – nose; B – vibrissae; C – lips; D – tongue; G – chin; J – jaw; E – neck; F – forelimb; H – hindlimb; I – trunk; K – pinna

suppression of unitary discharges. However, all discharge suppressions evoked by ICMS will be here mentioned as "inhibitions". The effects of conditioning cortical stimulations on peripherally-evoked responses were not even tested. In fact, the repeated insertion in the skin of stimulating electrodes provoked trouble and hyperreactivity in turn disturbing the cellular activity and recordings.

*CT tests on VT neurons with vibrissa RFs*

A total of 29 cortical foci were stimulated. Their distribution in AGrl and Gr is reported in Fig. 2A (see also Table 1).

Out of the 86 VT neurons reactive to displacement of vibrissae, 23 were assayed for stimulation of single foci evoking vibrissa movements; these foci were located in the vibrissa area of AGrl (15 neurons) and Grl (8 neurons). A sample of 39 neurons was tested for stimulation of two different foci (one in AGrl and another in Grl) both evoking vibrissa movements. The remaining 24 neurons were tested by stimulating single foci (in AGrl, Grm and Grl) evoking limb movements. Since a relevant number of neurons ($n = 39$) was tested for stimulation of two different foci, a total of 125 CT tests was performed.

Neuronal responses were obtained following stimulation of vibrissa foci which were located in either AGrl or Grl. A significant number of responses was observed only when the vibrissa RF overlapped or was closely adjacent to region of the cortically-evoked movement (Fig. 3). In these conditions, the percentage of effective CT tests was significantly higher when stimulating Grl (87% of 39 tests) than AGrl (74% of 47 tests). Instead, responses were rarely observed when neuronal RF lay distant from the vibrissa moved following ICMS (Fig. 4D).

The response pattern was mostly excitatory either when RF was centered on the region of motor target (93% in AGrl and 88% in Grl) or when it was closely adjacent (89% in AGrl and 84% in Grl). These results are illustrated in Fig. 3 (see also Figs. 4 and 7A). It is interesting to note that the convergence of facilitatory effects from AGrl and Gr was found when both foci had the same motor target (Fig. 4G, H). Suppression of cellular activity was rarely observed. In a few instances, the discharge of VT neurons, which was evoked by pro-

**Table 1.** Distribution of stimulated foci in the lateral part of the agranular cortex (AGrl), in the lateral (Grl) and medial part (Grm) of the granular cortex to test the reactivity of VT neurons with vibrissa or limb receptive fields (RF). The number of foci and tests performed for each representation area is shown

| Cortical representation area | | Cortical stimulation | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | AGrl | | | Grm | | Grl | | |
| | | Vibrissa | Forelimb | Hindlimb | Forelimb | Hindlimb | Vibrissa | Forelimb | Hindlimb |
| Neurons with vibrissa RF | number of foci | 11 | 1 | – | 2 | 1 | 12 | 1 | 1 |
| | number of tests | 54 | 5 | – | 6 | 4 | 47 | 5 | 4 |
| Neurons with limb RF | number of foci | – | 6 | 5 | 11 | 9 | – | 4 | 4 |
| | number of tests | – | 17 | 11 | 45 | 26 | – | 20 | 14 |

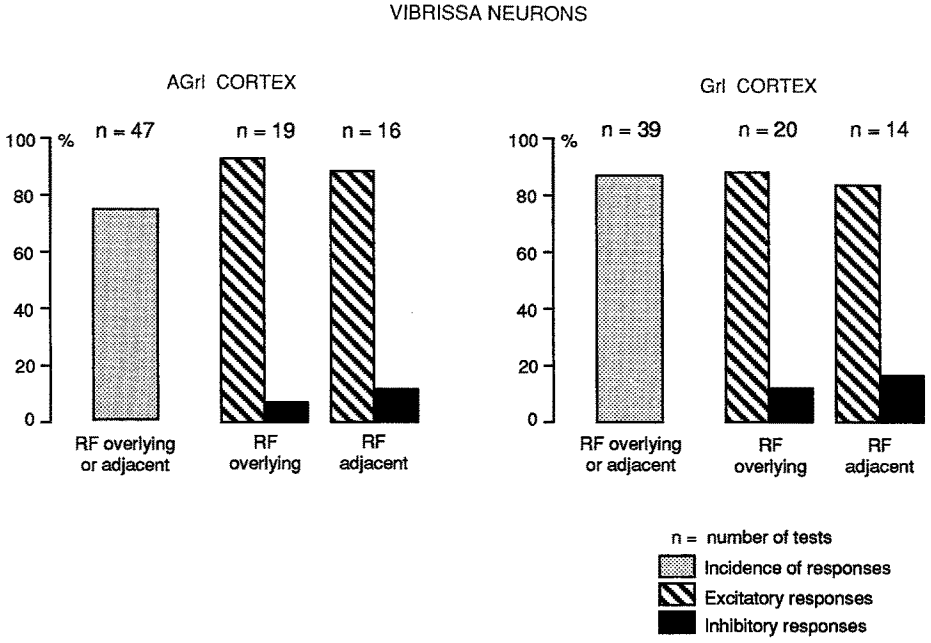
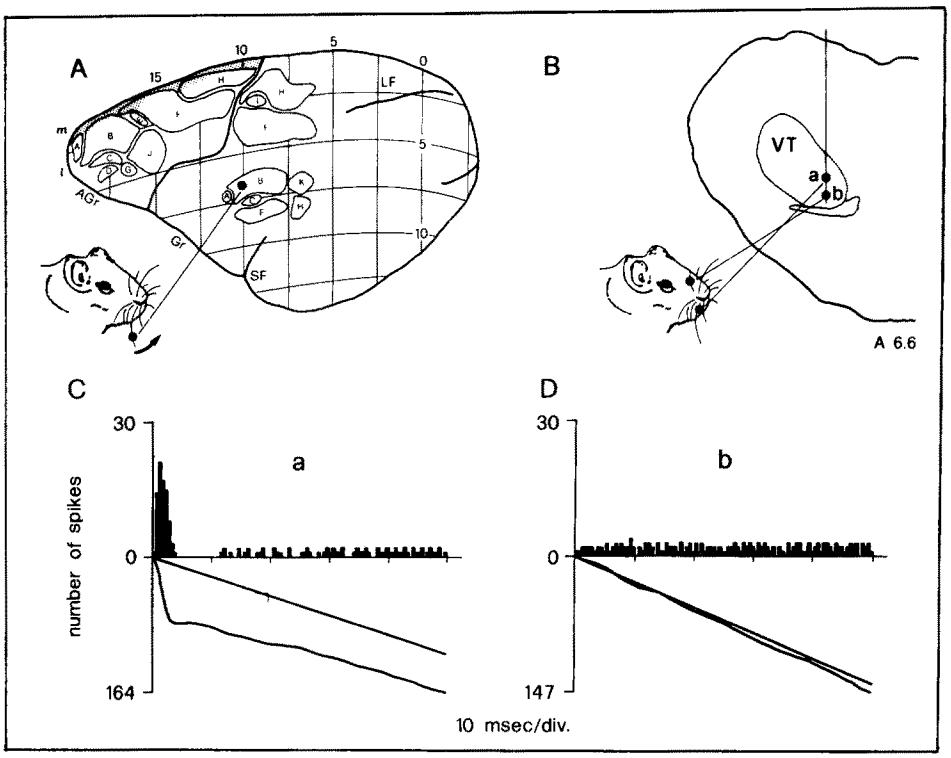



**Fig. 3.** Incidence and pattern of responses of VT neurons with vibrissa receptive field (RF) which were tested for stimulation of cortical sites in the vibrissa representation areas of the agranular and granular cortex. The numbers on the columns illustrating the incidence of responses indicate the totality of tests which were performed on neurons having RFs overlying or adjacent to the cortical motor target. The numbers on the columns showing the pattern of responses exclusively refer to the effective tests. Note the preeminence of excitatory responses of units having RF either overlying or closely adjacent to the cortical motor target. AGrl – lateral part of the agranular cortex; Grl – lateral part of the granular cortex



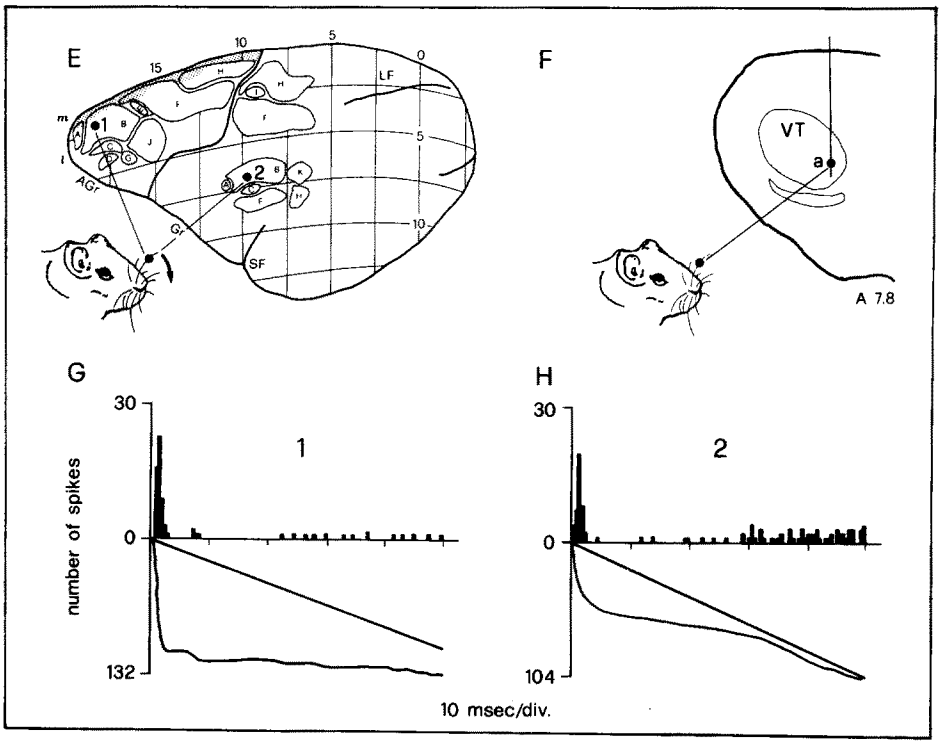




**Fig. 4A–H.** Responses of thalamocortical vibrissa neurons evoked by stimulating cortical foci in the vibrissa representation areas in two separate experiments. *Upper panel* – **A** *filled circles* indicate the location of the stimulating site in the granular cortex yielding movement of a single vibrissa as marked in the figurine. Conventions as in Fig. 2. **B** camera lucida showing reconstruction of the microelectrode track along which two VT neurons (a, b), each specifically activated by displacement of a single vibrissa (*filled circles* in the figurine), were recorded. **C, D** post stimulus time histograms and cumulative frequency distributions obtained by testing the two VT neurons for stimulation of the cortical focus marked in **A**. Note that excitatory responses were only observed for the neuron a, whose receptive field overlapped the cortical motor target, but not for the neuron b which had a distant receptive field. *Lower panel* – **E** *filled circles* indicate the location of two stimulated sites (1 and 2) in the agranular and granular cortex, both evoking movement of the same vibrissa, as marked in the figurine. Conventions as in Fig. 2. **F** camera lucida showing reconstruction of the microelectrode track along which one VT neuron (a) was recorded; this neuron was activated by the same vibrissa which was moved by stimulation of both cortical sites. **G, H** post stimulus time histograms and cumulative frequency distributions show that convergent excitatory responses were obtained by stimulating both cortical foci

longed natural stimulation of the vibrissa region, was significantly suppressed (duration: 40–80 ms) by ICMS. Excitatory responses induced by stimulation of AGrl occurred at latencies ranging from 1.5 to 6.4 ms (70% of responses with latencies between 2.0 and 3.5 ms). Excitations following stimulation of Grl appeared after 1.6–7.0 ms (71% with latencies of 2.0–4.0 ms). No significant differences in mean latency values were found between responses of AGrl and Gr (3.35 ms +/− 1.6 S.D. and 3.38 ms +/− 1.71 S.D.). Discharge increases lasted 4.0–12.5 ms and were often followed by a period of inhibition (duration: 25–60 ms) of spontaneous spikes. The latencies of early inhibitory responses after stimulation of either AGrl or Grl ranged between 1.7 and 7.9 ms (66% of responses with latencies of 3.0–5.0 ms). Inhibitory responses lasted 30–60 ms. Stimulation of foci con-

trolling limb movements never modified the discharges of vibrissa units.

*CT tests on VT neurons with limb RFs*

Figure 2B and Table 1 illustrate distribution of the 39 cortical foci which were isolated to perform CT tests on 96 limb VT neurons. Of these neurons, 59 were tested with stimulation of single cortical foci and 37 for separate stimulation of two different foci. Among the 59 neurons, 16 were assayed for ICMS of limb areas of AGrl and the remaining 43 for ICMS of limb areas of Grm. The sample of 37 neurons tested with stimulation of pairs of cortical foci evoking limb movements were given in different combinations: *i*) two foci located in Grm (3 neurons); *ii*) one focus in AGrl and one in Grl (12 neurons); *iii*) one focus in Grm and another in Grl (22 neurons). Since these 37 neurons were tested for stimulation of two different cortical sites, a total of 133 CT tests was performed on 96 neurons.

Marked differences were observed by comparing the results of CT tests by stimulating AGrl and Gr. ICMS of AGrl rarely modified discharges of the tested VT neurons (4% of 28 tests; Fig. 6A, B, F–H). Figure 5 shows that ICMS of Grm and Grl yielded a very high incidence of responses when the RF of a neuron was located in a cutaneous limb region overlying or adjacent to the joint moved by the stimulated cortical focus; the responsiveness was somewhat higher upon ICMS in Grm than in Grl. In fact, the percentage of responses to forelimb foci was 88% of 40 tests in Grm and 73% of 17 tests in Grl; the percentage of responses to hindlimb foci was 80% of 20 tests in Grm and 71% of 10 tests in Grl. Concerning the nature, excitatory or inhibitory, of responses of fore- and hindlimb neurons, Fig. 5 also shows that the response pattern of forelimb neurons strictly depended on the spatial relationship between the location of the neuronal RF and cortical target; in about 95% of cases the responses to ICMS in both Grm and Grl were excitatory when the RF was overlying the region of the movement (see also Fig. 6A, B, E), while inhibitory responses were observed (96%) when the RF was adjacent to the moved region (Fig. 6A, B, D). Instead, the responses of hindlimb neurons to stimulation of both Grm

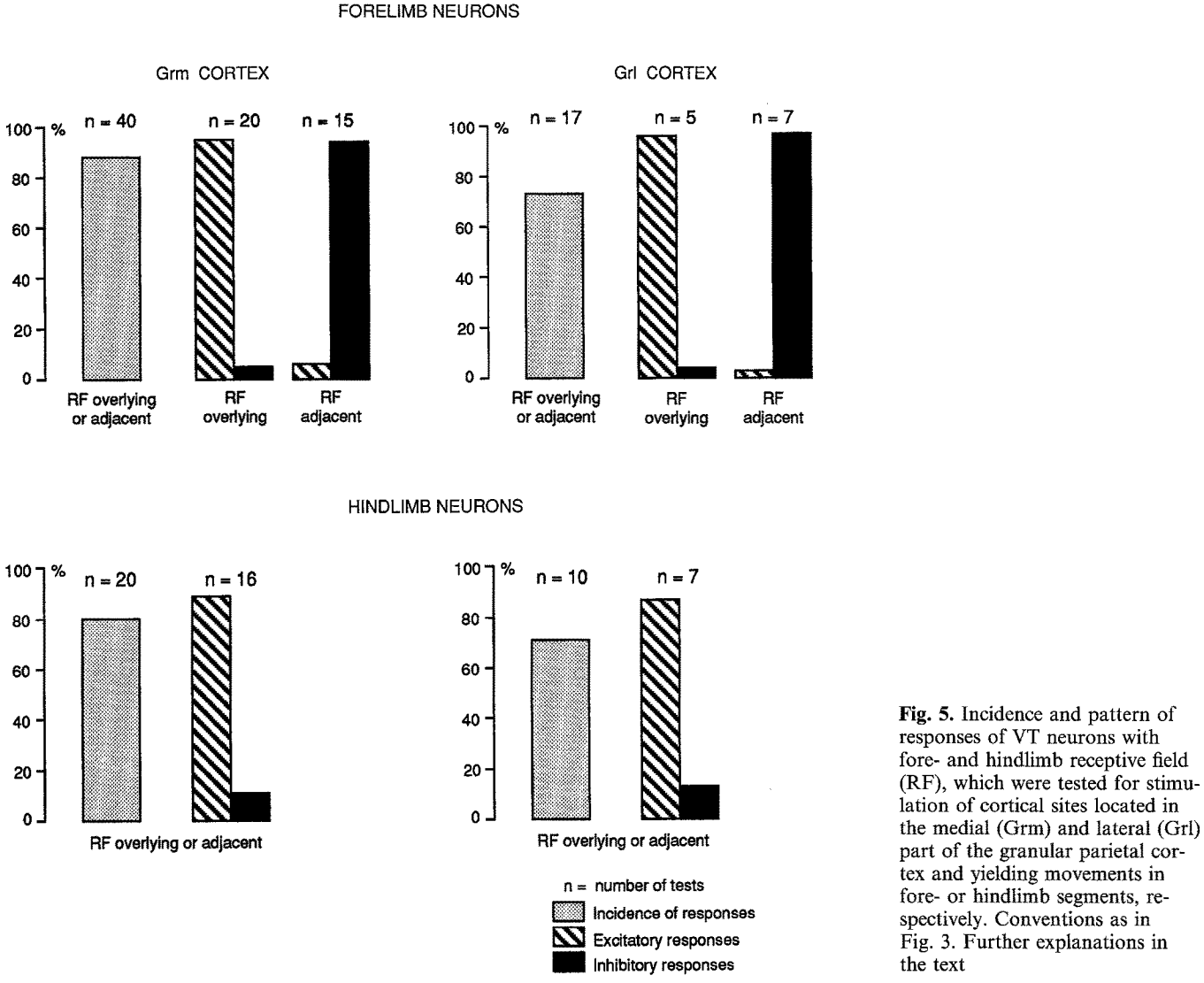



**Fig. 5.** Incidence and pattern of responses of VT neurons with fore- and hindlimb receptive field (RF), which were tested for stimulation of cortical sites located in the medial (Grm) and lateral (Grl) part of the granular parietal cortex and yielding movements in fore- or hindlimb segments, respectively. Conventions as in Fig. 3. Further explanations in the text

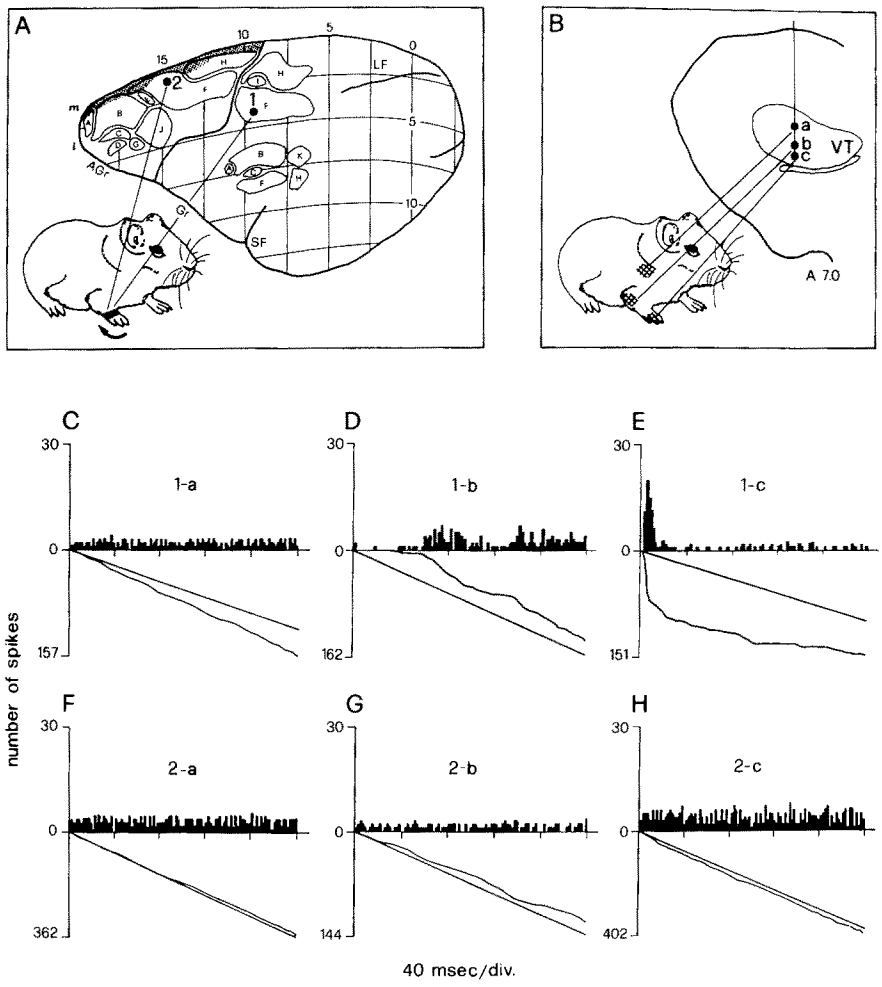



**Fig. 6.** Responses of three forelimb VT neurons (a, b, c) to stimulation of two foci in forelimb representation area of the agranular and granular cortex. **A** *filled circles* indicate the location of foci 1 and 2 both evoking wrist flexion (see figurine inset). Conventions as in Fig. 2. **B** neurons a, b, and c recorded along the penetration in VT had a receptive field which was distant (a), adjacent to (b) or overlapping (c) with respect to the motor target of both cortical foci. In panels **C–H,** the number and letter over post stimulus histograms and cumulative frequency distributions indicate the stimulating focus and the tested neuron for each cortico-thalamic test. Note that stimulation of focus 1 only evoked responses of the neuron b and c, with inhibitory and excitatory effects, respectively; none of the three neurons was influenced by stimulation of focus 2

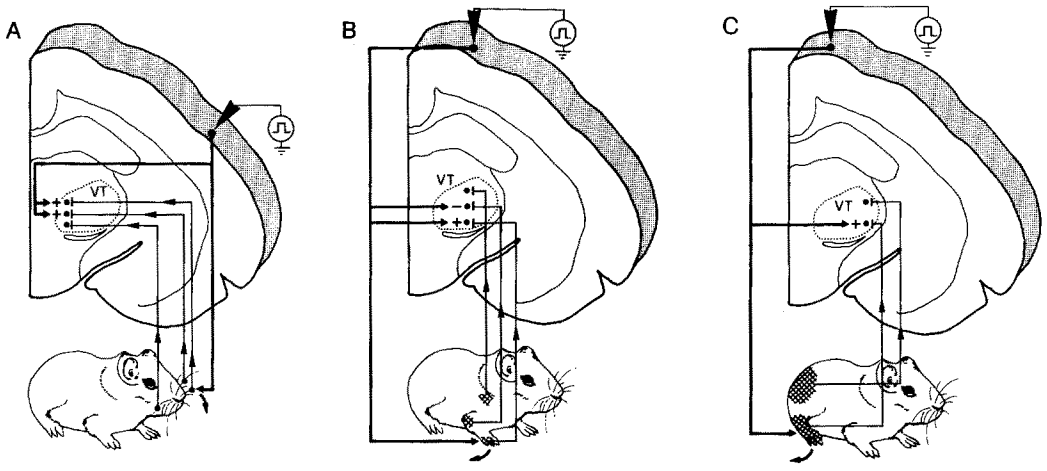



**Fig. 7.** Schematic representation of the organization of cortical influences on VT neurons relaying to the cortex somatosensory messages concerning vibrissae and limbs, according to the results of the present work. Thalamo-cortical linkages are not indicated in the scheme. **A** activation of a cortical focus controlling movements of a given vibrissa excites the VT neurons receiving information from the same vibrissa or from adjacent ones, while it does not affect neurons relaying information from distant vibrissae. **B** cortical modulation from a focus controlling movements of a given forelimb joint only concerns VT units whose receptive fields overlap or are adjacent to the same joint; in the two cases, the cortical influences are excitatory or inhibitory, respectively. This organization recalls the scheme of the "surround inhibition". **C** cortical hindlimb foci excite VT units receiving messages from receptive fields which include the joint moved by the cortex activation, but they do not influence neurons sensitive to stimulation of regions distant from the cortical motor target

and Grl were excitatory in about 88% (inhibitory in the remaining 12%) of the tests on neurons with RF either overlapping or adjacent to the cortical motor target (Fig. 5). A very low incidence of responses (3%) was observed in 18 tests in which the RF of both fore- and hindlimb neurons was distant from the joint moved by ICMS of Grm and Grl (see Fig. 6A–C). The Fig. 7B, C schematically illustrates the nature of cortical control on limb VT neurons, according to the pooled results of the present study.

Latency values of excitatory responses of both fore- and hindlimb neurons to stimulation of limb foci in Grm and Grl ranged from 1.4–6.6 ms (71% of responses with latencies between 2.0–4.0 ms) and from 1.5–7.5 ms (66% with latencies of 2.0–4.5 ms), respectively. The duration of these excitations was 5–16 ms. A period of discharge suppression (10–70 ms) often followed excitatory responses. Early inhibitory responses upon stimulation of Grm and Grl appeared at latencies of 2.0–7.2 ms in forelimb neurons (75% with latencies of 3.0–5.0 ms) and 1.9–6.8 ms (71% at 3.0–5.5 ms) in hindlimb neurons; the duration of inhibitory responses for fore- and hindlimb units ranged between 25 and 70 ms.

## Discussion

The results of the present study demonstrate that VT neurons relaying somatosensory messages to the cortex can be influenced by ICMS without any involvement of afferent pathways from somatic periphery. In fact, the stimulus strengths which were utilized to test VT neurons were far below the threshold for evoking vibrissa or limb movements. Moreover, the latency values of cortically-induced VT responses were too short to be ascribed to activation via a trans-peripheral loop.

Instead, an involvement of a cortico-dorsal column nuclei-thalamic route or, respectively, of a cortico-trigeminal nucleus-thalamic route could be taken in account, but only concerning the responses at the longest latency values. Actually, given the range of latency values of the excitatory responses (1.4–6.6 ms) there might be a mixture of direct and indirect effects on VT neurons.

Thalamo-cortical transmission of the exteroceptive information from vibrissae and limbs appears to be modulated by cortical regions receiving an exteroceptive input which arises from the same body regions (Rapisarda et al. 1990).

VT neurons activated by vibrissa RFs are submitted to a dual control arising from two regions, one in AGrl and another in Gr, which in turn receive exteroceptive messages from vibrissae. The control exerted by AGrl appears to be somewhat less marked, as suggested by the lower incidence of responses of VT neurons following stimulation of AGrl foci than Gr ones (74% vs. 87%). This result could be related to the less homogeneous organization of the vibrissa area in AGrl, at least concerning modalities of peripheral stimulation which influence this area. In fact, the foci which receive exteroceptive input in AGrl are intermingled with foci which are influenced by proprioceptive stimulation (Rapisarda et al. 1990). Thus, the lower incidence of positive CT tests from AGrl could be explained by the fact that ICMS was performed in an area where exteroceptive foci are less packed. On the other hand, the existence in the Gr vibrissa area of foci which are all driven by exteroceptive input (Rapisarda et al. 1990) could account for the higher incidence of thalamic responses, so suggesting a stronger control on VT units. This more effective control could reflect the detailed organization of the barrel cortex which, as suggested by Hoogland et al. (1987), represents a specific anatomical substrate able to ensure not only a very precise somatotopy of the sensory vibrissa function, but also a selective control on VB neurons with vibrissa RF.

Ascending information from limb skin appears to be only submitted to the modulatory action of Gr, which is driven by a "pure" exteroceptive input (Rapisarda et al. 1990). Conversely, the limb area in AGrl, only receiving proprioceptive input, seems to be not involved in the modulation of exteroceptive signals, since ICMS in this agranular area rarely yielded responses of TCR VT neurons having cutaneous limb RF. This "motor" area very probably controls the ventrolateral thalamic nucleus (VL) which is known to relay proprioceptive messages to the motor cortex (see Jones 1985 for a review). Short latency responses of VL units to ICMS of AGrl were observed during sporadic recordings of proprioceptive neurons belonging to this nucleus. Moreover, the possibility of a distinct modulatory control exerted from Gr on exteroceptive VT relay neurons and from AGr on proprioceptive ones is supported by similar conclusions concerning the cortico-thalamic regulation of somatosensory input in the rat (see Shin and Chapin 1990).

### *Cortical control on VT vibrissa neurons*

The observation of mostly excitatory cortical influences on vibrissa VT neurons is intriguing. In fact, stimulation of a focus yielding movement of a single vibrissa not only excited VT cells activated by displacement of the same vibrissa, but also units receiving signals from adjacent vibrissae. The existence of such a divergent excitatory cortico-thalamic control is supported, at least concerning Gr, by the findings of Hoogland et al. (1987) in mice. These Authors clearly demonstrated that cortico-thalamic projections originating from one cortical barrel column are not restricted to the corresponding "barrelloid" in VB, but they contact a full arc of barrelloids.

In the present study the strongest thalamic responses along each penetration were obtained when ICMS was carried out at level of layer V; thus, the stimulating current could efficiently activate the somata in layer V or the apical dendritic tree of layer VI neurons. Moreover, the assumption that cortical control on VT neurons can originate from the deepest cortical layers is supported by results of anterograde and retrograde transport studies in rats (Jacobson and Trojanowski 1975; Rustioni et al. 1983; Chmielowska et al. 1989) and in guinea pigs (Giuffrida et al. 1989) showing a large number of retrogradely labelled neurons in layers V and VI after tracer injections in VB.

Concerning the almost exclusively excitatory cortical control on VB vibrissa neurons seen in our study, it is interesting to note that inhibitory corticofugal effects on sensory vibrissa units were previously seen in rats by Woolston et al. (1983). These Authors demonstrated that stimulation of sensorimotor cortex sites, which were activated by mechanical stimulation of vibrissae, yielded excitatory phenomena on trigeminal neurons with vibrissa RFs including that of the cortical stimulating locus; conversely, inhibition only occurred in neurons whose RF did not correspond to that of the stimulating locus. The comparison of our findings with those of Woolston et al. (1983) suggests a different modality of cortical control on signal transmission at the level of third- and second-order neurons of the ascending somatosensory system. On the other hand, these differences are supported by the distinctive anatomical organization of divergent cortico-VB projections vs. the point-to-point cortico-trigeminal projections described in mice (Hoogland et al. 1987; Welker et al. 1988).

*Cortical control on VT limb neurons*

Our findings indicate that the cerebral cortex influences the transmission of signals coming from fore- or hindlimb in a different way. In fact, ICMS of single forelimb motor foci in Gr specifically excited or inhibited forelimb VT neurons according to whether their RF overlapped or, respectively, was adjacent to the cortical motor target. Instead, excitations were mainly displayed by hindlimb neurons which were tested for ICMS of hindlimb foci. It is likely that such a distinctive cortical control could be related to the spatial characteristics of RFs of the fore- and hindlimb VT neurons, *i.e.* the former have much more restricted RFs than the latter. In functional terms, the forelimb neurons would receive a punctiform control from restricted movement-evoking cortical areas while the hindlimb neurons would be submitted to a less detailed cortical influence. Indeed, since the RFs of hindlimb neurons were very wide, it was not possible to identify RFs which lay adjacent to the motor target.

The finding that the appearance of excitations or inhibitions of forelimb neurons was strictly related to the location of neuronal RF, with respect to that of the evoked limb movement, could help resolve the apparently contradictory hypotheses which were previously made about the overall nature, facilitatory or inhibitory, of the cortico-thalamic control in cats and rats. In fact, several data from experiments of cortical stimulation or spreading depression on single ventrobasal neurons have provided evidence for facilitation (Waller and Feldman 1967; Andersen et al. 1972; Albe-Fessard et al. 1983; Yuan et al. 1985, 1986; Aicardi et al. 1988), inhibition (Ogden 1960; Hosko and Helm 1969; Burchfiel and Duffy 1974) or both effects (Iwama and Yamamoto 1961; Shimazu et al. 1965; Tsumoto et al. 1975). In our opinion, the experimental approach used in the present study allows us to demonstrate the coexistence of well organized facilitatory and suppressory modulatory actions of cortical motor foci on limb VT units. This idea seems to be supported by analogous findings from preliminary observations on the cortico-VPL control in cats (Giuffrida et al. 1988).

The present experiments did not allow us to demonstrate, in a direct way, the existence of cortico-thalamo-cortical closed neuronal loops specifically concerning single movement-evoking cortical foci; such a loop could be the functional equivalent of the reciprocal connection between single SI columns and punctate groupings of VB cells in the primate (Jones et al. 1979) and rat (Saporta and Kruger 1977).

A possibility exists that the cortico-VT effects could be mediated by collateral fibers of corticospinal projections as seen in the cat by Giuffrida et al. (1983a) but at the present no data are available about the relevance of such collaterals in the guinea pig and the issue still remains unresolved.

*General considerations*

The possible functional meaning of the cortical control on VT neurons can be examined by analyzing the incidence and pattern of responses of VT neurons to ICMS with reference to the spatial relation between the cortical motor target and RF of tested neurons.

Two main findings indicate that this control is organized in a very precise manner. 1) The probability of a VT neuron being influenced by ICMS depended on whether its RF was overlying or strictly adjacent to the region of the cortically evoked movement. This could mean that the outflow of a cortical focus, triggering movements of any one restricted body region, specifically influences the ascending transmission of sensory signals which originate from the same region. 2) The distribution of response pattern indicates that the cerebral cortex modulates the transmission of messages from vibrissae in a manner different to those from limbs. In fact, the responses of VT neurons with vibrissa RF were predominantly excitatory, independently of whether the RF was overlapping or adjacent to the motor target, while limb neurons displayed excitatory or inhibitory effects when the RF overlapped or was adjacent to the motor target, respectively.

From a functional point of view, the excitatory nature of the cortical control on TCR vibrissa neurons suggests that a cortical signal inducing movement of a single vibrissa can activate mechanisms of sensory-motor integration at thalamic level, capable of enhancing the afferent transmission of somatosensory messages concerning the same vibrissa and also neighbouring whiskers. Since vibrissa neurons are submitted to a convergent modulatory control from both Grl and AGrl, it may be inferred that the mechanisms of vibrissa sensory-motor integration operate at thalamic level in a more complex manner than the cortical modulation of limb sensitivity, for they utilize signals emanating from two areas which differ in terms of cytoarchitectonic features and functional organization (Rapisarda et al. 1990). Another interesting hypothesis about the significance of the cortical control, at least concerning Grl, was advanced

in previous neuroanatomical studies (Hoogland et al. 1987; Welker et al. 1988). According to this hypothesis, a sensory volley evoked by stimulation of a particular vibrissa, would enhance the activity of the corresponding TCR vibrissa neuron, via a reverberating trans-cortical loop involving single barrel columns. On the other hand, the procedures of ICMS adopted in the present study allow us to believe that sensory thalamic units can be modulated by descending motor commands, even without a primitive activation of somatosensory afferents. The two hypotheses are not mutually exclusive, since the mechanisms of cortico-thalamic modulation could be started by either motor or sensory signals.

The functional meaning of the excitatory effects on limb neurons could be analogous to that suggested for the cortical modulation of vibrissa sensitivity. The observation that forelimb neurons showed inhibitions when their RF was adjacent to the cortical motor target, suggests that the messages ascending from forelimb would be further amplified by simultaneous inhibition of thalamic neurons forwarding to the cortex somatosensory information from adjacent segments. As a matter of fact, the amplification of these messages would be the result of a "descending" surround inhibition which would increase the ratio signal/noise of the afferent volleys through somatosensory transmission systems, as hypothesized by Levitt et al. (1964). From a behavioural point of view, such an optimization of sensitivity could provide a major contribution to the manipulative function of the forelimb.

The conclusion that a motor command can induce an early improvement of the reactivity of thalamic neurons, relaying to the cortex information from the body region which will be involved in the ongoing movement, is consistent with our preliminary reports from similar experiments in VB and DCN of chronically-implanted cats (Giuffrida et al. 1983b, 1984, 1988). On the contrary, a reduction of the exteroceptive input to VB has been reported by observing decreases of evoked lemniscal potentials during performance of movements in the cat and man (Ghez and Lenzi 1971; Ghez and Pisa 1972; Coulter 1974; Coquery 1978; Pompeiano 1982). The two opposite conclusions may arise from the different methodological approaches which were employed. The functional hypothesis we suggest derives from the analysis of changes of the basal activity of single VT neurons following ICMS. The technique of conditioning cortical stimulations on peripherally-evoked VT responses, which could contribute to clarifying the mechanisms of cortico-thalamic modulation has not be used in the present study because it requires the use of anaesthetic drugs, a condition that increases the appearance of inhibitions (Giuffrida et al. 1985; Mayer and Westbrook 1987; Shin and Chapin 1989, 1990).

*Acknowledgements.* The Authors are grateful to Salvatore Bentivegna and Stefania Monti for help in preparing the illustrative material, Giuseppe Mancinelli for construction of a device converting biological signals and Leonida Sabattini for arranging the chronic implantation system. This work was supported by grants from the Consiglio Nazionale delle Ricerche and Ministero della Pubblica Istruzione (Italy).

## References

Aicardi G, Giuffrida R, Rapisarda C, Albe-Fessard D (1988) Cortical control on ventral thalamus neurons investigated in the guinea pig by spreading depression technique. Neurosci Lett (Suppl) 33:S63

Albe-Fessard D, Condés-Lara M, Kesar S, Sanderson P (1983) Tonic cortical controls acting on spontaneous and evoked thalamic activity. In: Macchi G, Rustioni A, Spreafico R (eds) Somatosensory integration in the thalamus. Elsevier, Amsterdam, pp 273–285

Andersen P, Junge K, Sveen O (1972) Cortico-fugal facilitation of thalamic transmission. Brain Behav Evol 6:170–184

Burchfiel JL, Duffy FH (1974) Corticofugal influences upon cat thalamic ventrobasal complex. Brain Res 70:395–411

Chapin JK, Lin CS (1984) Mapping of the body representation in the SI cortex of anaesthetized and awake rats. J Comp Neurol 229:199–213

Chmielowska J, Carvell GE, Simons DJ (1989) Spatial organization of thalamocortical and corticothalamic projection systems in the rat SmI barrel cortex. J Comp Neurol 285:325–338

Coquery JM (1978) Role of active movement in control of afferent input from skin in cat and man. In: Gordon G (ed) Active touch: the mechanism of recognition of objects by manipulation. Pergamon Press, Oxford, pp 161–169

Coulter JD (1974) Sensory transmission through lemniscal pathway during voluntary movement in the cat. J Neurophysiol 37:831–845

Emmers R (1987) Somesthetic system of the rat. Raven Press, New York

Ghez C, Lenzi GL (1971) Modulation of sensory transmission in cat lemniscal system during voluntary movement. Pflügers Arch 323:273–278

Ghez C, Pisa M (1972) Inhibition of afferent transmission in cuneate nucleus during voluntary movement in the cat. Brain Res 40:145–151

Gioanni Y (1987) Cortical mapping and laminar analysis of the cutaneous and proprioceptive inputs from the rat foreleg: an extra- and intra-cellular study. Exp Brain Res 67:510–522

Giuffrida R, Li Volsi G, Pantò MR, Perciavalle V, Urbano A (1983a) Pyramidal influences on ventral thalamic nuclei in the cat. Brain Res 279:254–257

Giuffrida R, Palmeri A, Perciavalle V, Sapienza S (1983b) Influenze della corteccia pericrociata su neuroni del nucleo cuneato principale nel gatto. Proc XXXV Congr Naz Soc It Fisiol: 220

Giuffrida R, Palmeri A, Ricca G, Sapienza S (1984) Pericruciate cortex control on gracile neurons in the cat. Neurosci Lett (Suppl) 18:S302

Giuffrida R, Sanderson P, Sapienza S (1985) Effect of microstimulation of movement-evoking cortical foci on the activity of neurons on the dorsal column nuclei. Somatosens Res 2:237–247

Giuffrida R, Palmeri A, Ricca G, Sapienza S (1988) Cortical control on exteroceptive relay thalamic neurons in the cat. Pflügers Arch 412:S27

Giuffrida R, Aicardi G, Sapienza S, Rapisarda C (1989) Studio topografico e immunocitochimico delle proiezioni corticotalamiche e corticorubrali nella cavia. Proc XLI Congr Naz Soc It Fisiol:176

Harris RM, Hendrickson AE (1987) Local circuit neurons in the rat ventrobasal thalamus. A GABA immunocytochemical study. Neuroscience 21:229–236

Hoogland PV, Welker E, Van der Loos H (1987) Organization of the projections from barrel cortex to thalamus in mice studied with *Phaseolus vulgaris*-leucoagglutinin and HRP. Exp Brain Res 68:73–87

Hosko MJ, Helm FC (1969) Augmentation of the somatosensory thalamic response by "local" cerebral ischemia. Life Sci 8:301–306

Iwama K, Yamamoto C (1961) Impulse transmission of thalamic somatosensory relay nuclei as modified by electrical stimulation of the cerebral cortex. Jpn J Physiol 11:169–182

Jacobson SJ, Trojanowski JQ (1975) Corticothalamic neurons and thalamocortical terminal fields: an investigation in rat using horseradish peroxidase and autoradiography. Brain Res 85:385–401

Jones EG (1985) The thalamus. Plenum Press, New York

Jones EG, Wise SP, Coulter JD (1979) Differential thalamic relationships of sensory-motor and parietal cortical fields in monkeys. J Comp Neurol 183:833–881

Lamour Y, Jobert A (1982) Laminar distribution and convergence of deep and superficial peripheral inputs in the forelimb representation of rat SI somatosensory cortex. J Physiol (Paris) 78:158–162

Levitt M, Carreras M, Liu CN, Chambers WW (1964) Pyramidal and extrapyramidal modulation of somatosensory activity in gracile and cuneate nuclei. Arch Ital Biol 102:197–229

Mayer ML, Westbrook GL (1987) The physiology of excitatory amino acids in the vertebrate central nervous system. Progr Neurobiol 28:197–276

Ogden TE (1960) Cortical control of thalamic somatosensory relay nuclei. Electroencephalogr Clin Neurophysiol 12:621–634

Pompeiano O (1982) Inhibition of sensory transmission in the cat lemniscal system during fast movements: a review. Isr J Med Sci 18:105–118

Rapisarda C, Bacchelli B (1977) The brain of the guinea pig in stereotaxic coordinates. Arch Sci Biol 61:1–37

Rapisarda C, Palmeri A, Sapienza S (1986a) Influences of the granular parietal cortex on single thalamic neurons of the nucleus ventralis posterior (VP), in the chronic awake guinea pig. Proc XXX Congr Int Un Physiol Sci 16:P261.29

Rapisarda C, Palmeri A, Sapienza S (1986b) The response of neurons of the ventralis posterior thalamic nucleus to microstimulation of granular and agranular cortex in the guinea pig. Neurosci Lett (Suppl) 26:S117

Rapisarda C, Palmeri A, Sapienza S (1987a) Effects of microstimulation of the granular parietal cortex on sensory relay units of nucleus ventralis posterior, in the guinea pig. Pflügers Arch 408:S42

Rapisarda C, Palmeri A, Sapienza S (1987b) Cortico-thalamic modulation of exteroceptive somatic information, in the guinea pig. Proc Sat Symp on "Cellular thalamic mechanisms", II Congr IBRO:S80

Rapisarda C, Palmeri A, Sapienza S (1988) Influences of the agranular and granular cortex on thalamic units relaying sensory messages from the face region, in the guinea pig. Pflügers Arch 412:S29

Rapisarda C, Palmeri A, Aicardi G, Sapienza S (1990) Multiple representations of the body and input-output relationships in the agranular and granular cortex of the chronic awake guinea pig. Somatosens Mot Res 7:289–314

Rustioni A, Schmechel DE, Spreafico R, Cheema S, Cuenod M (1983) Excitatory and inhibitory amino-acid putative neurotransmitters in the ventral posterior complex: an autoradiographic and immunocytochemical study in rats and cats. In: Macchi G, Rustioni A, Spreafico R (eds) Somatosensory integration in the thalamus. Elsevier, Amsterdam, pp 365–383

Saporta S, Kruger L (1977) The organization of thalamocortical relay neurons in the rat ventrobasal complex studied by the retrograde transport of horseradish peroxidase. J Comp Neurol 174:187–208

Shimazu H, Yanagisawa N, Garoutte B (1965) Cortico-pyramidal influences on thalamic somatosensory transmission in the cat. Jpn J Physiol 15:101–124

Shin HC, Chapin JK (1989) Mapping the effects of motor cortex stimulation on single neurons in the dorsal column nuclei in the rat: direct responses and afferent modulation. Brain Res Bull 22:245–252

Shin HC, Chapin JK (1990) Mapping the effects of motor cortex stimulation on somatosensory relay neurons in the rat thalamus: direct responses and afferent modulation. Brain Res Bull 24:257–265

Sievert CF, Neafsey EJ (1986) A chronic unit study of the sensory properties of neurons in the forelimb areas of rat sensorimotor cortex. Brain Res 381:15–23

Tsumoto T, Nakamura S, Iwama K (1975) Pyramidal tract control over cutaneous and kinesthetic sensory transmission in the cat thalamus. Exp Brain Res 22:281–294

Waller HJ, Feldman SM (1967) Somatosensory thalamic neurons: effects of cortical spreading depression. Science 157:1074–1077

Welker E, Hoogland PV, Van der Loos H (1988) Organization of feedback and feedforward projections of the barrel cortex: a PHA-L study in the mouse. Exp Brain Res 73:411–435

Woolston DC, La Londe JR, Gibson JM (1983) Corticofugal influences in the rat on responses of neurons in the trigeminal nucleus interpolaris to mechanical stimulation. Neurosci Lett 36:43–48

Yuan B, Morrow TJ, Casey KL (1985) Responsiveness of ventrobasal thalamic neurons after suppression of SI cortex in the anaesthetized rat. J Neurosci 5:2971–2978

Yuan B, Morrow TJ, Casey KL (1986) Corticofugal influences of SI cortex on ventrobasal thalamic neurons in the awake rat. J Neurosci 6:3611–3617