Brain Research, 631 (1993) 241–246

BRES 19525

Spinothalamocortical projections to the secondary somatosensory cortex (SII) in squirrel monkey

Richard T. Stevens *, Susan M. London, A. Vania Apkarian

Department of Neurosurgery, Neurosurgery Research Center, Weiskotten Hall, Rm 3118, SUNY Health Science Center, Syracuse, NY 13210, USA

(Accepted 27 July 1993)

Key words: Thalamocortical; Spinal cord; Ascending projection; Nociceptive; Pain

Anterograde labeling of the cervical spinothalamic tract was combined with retrograde labeling of thalamocortical cells projecting to the hand region of the second somatosensory cortex (hSII) to identify likely sites in the thalamus for processing and transmitting nociceptive information to hSII. Anterograde labeling of terminals was done with 2% WGA-HRP injections in the cervical enlargement; thalamocortical cells were retrogradely labeled with fluorescent tracers. In one experiment, the contralateral primary somatosensory cortex hand region (hSI) was injected to provide a direct comparison with hSII thalamic label. Both labeled cells and terminal-like structures were visualized in single thalamic sections and their numbers and positions quantitatively analyzed. The number of labeled cells within 100 microns from the STT terminals were counted as overlapping cells. Four thalamic nuclei, ventroposterior inferior (VPI), ventroposterior lateral (VPL), posterior nucleus (PO) and centrolateral nucleus (CL) combined to contain 86.5% of all hSII-projecting overlapping cells. Of all hSII-projecting thalamic overlapping cells, VPI contained the largest number (36.4% of the total) followed by the anterior portion of the posterior nuclear complex (POa; 20.4%), VPL (18.3%) and CL (11.4%). Results of the hSI injection show a different pattern of overlap in agreement with our earlier study. The relative distribution of overlapping cells was dependent on the antero-posterior position of the SII injections. The most anterior injections resulted in small numbers of labeled cells, with the majority of overlapping cells located in PO and CL. The more posterior injections resulted in overlapping cells mainly in VPI and VPL. The results indicate that, in the squirrel monkey, VPI, VPL, POa and CL relay nociceptive information from the spinal cord to the second somatosensory cortex.

INTRODUCTION

The spinothalamic tract (STT), composed of over 18,000 neurons[1], is a major direct pathway mediating pain and temperature sensation to the thalamus, since more than 90% of these neurons encode cutaneous nociceptive stimuli as repeatedly demonstrated in the primate (for references see Willis and Coggeshall[33]). Therefore, the locations of the STT terminals can be used as a fingerprint for thalamic regions involved in processing of nociception. In evaluating the fine structure of STT and leminiscal terminations, Ralston et al.[26,27] and Ma et al.[22] have shown that most STT terminations are located on dendritic profiles usually within 100 μm of the soma of neurons presumed to be projecting to the cortex. Thus, thalamic neurons located within 100 μm of STT terminals are capable of receiving direct STT inputs and hence being involved in nociception. This relationship can be used to study the extent of the involvement of various cortical areas in nociception by combining retrograde thalamocortical labeling studies with anterograde STT labeling. With this approach, Gingold et al.[15] evaluated the proportion of identified primary somatosensory (SI) projecting cells capable of receiving STT inputs. The results showed that three distinct thalamic regions are involved in relaying of STT nociceptive information to SI; ventroposterior lateral (VPL), ventroposterior inferior (VPI) and centrolateral (CL) nuclei.

A small number of nociceptive responsive neurons have been described in the second somatosensory cortex in primates[10,11,31] and anatomic studies have shown that VPI is the major source of thalamic input to the region in addition to receiving inputs from VPL, Cl and PuLo[5,13,20,21]. In the current study, we used the overlap analysis method as described by Gingold et al.[15] to identify the thalamic regions capable of supplying nociceptive information from the cervical spinal

* Corresponding author. Fax: (1) (315) 464-5520.

cord via the spinothalamic tract to the hand region of SII (hSII).

MATERIALS AND METHODS

Twelve squirrel monkeys were used in this study. Data are presented from four of these. Data were not available or acceptable from eight animals due to technical reasons.

In all experiments, either 2% Diamidino Yellow (DY; $n = 1$), or 2% rhodamine beads (RB; $n = 3$) were used as retrograde tracers in hSII and 2% WGA-HRP was used as the anterograde tracer from the cervical enlargement (C_5–T_1). Animals were anesthetized with ketamine (25 mg/kg, i.m.) followed by Nembutal (20 mg/kg) and supplemented by doses of either ketamine (10 mg/kg/h, i.m.) or Nembutal (10 mg/kg/h, i.v.). Additionally, preventative medicines were routinely administered: Dilantin (.03cc, i.m.) for seizures, Decadron (0.03 cc, i.m.) for cerebral edema and atropine (0.07 cc, i.m.) for secretions. Under sterile conditions, a craniectomy was performed and electrophysiological recordings were made using low impedance parylene-coated tungsten microelectrodes to locate the hand region of SII (hSII). Electrode penetrations were made in a sterotaxic coronal plane but angled 40° in the sagittal axis. This penetration angle, previously described by Burton and Carlson[5], allowed access to the hand region of SII without passing through the hand region of SI. Only the medial most tracts had somatic receptive fields from surface (SI) recordings. These SI receptive fields were located on the chin. Using this technique, functionally equivalent regions of hSII were injected although the resultant AP values appeared to vary as subsequently determined from cytoarchitecture (Fig. 1B). Following functional identification of hSII, 4–7 injections were made (0.2 μl per site; Fig. 1B). In two animals (SL-9 and SL-12; Fig. 1A), the SI region dorsal to hSII was removed (by cauterization and by suction, respectively) prior to the SII injection to eliminate the possibility of SI contribution to thalamic labeling.

In one experiment (SL-6), in addition to the injection of SII with 2% RB, the ipsilateral hand region of SI was physiologically identified and injected with 2% Fluorogold (19 sites, 0.2 μl each site). By this means, comparisons could be made between the STT overlap with SI and SII within the same section when viewed with different fluorescent filters.

After completion of the cortical injections, a laminectomy was performed and the contralateral cervical enlargement was injected with 2% WGA-HRP (10 tracts, 2 sites per tract: one dorsal and one ventral, 0.1 μl per site). Following a 3-day survival time, animals were anesthetized and perfused transcardially with heparinized saline followed by 2.5% paraformaldehyde in 0.1M phosphate buffer. Tissue was sectioned (50 μm) and alternate sections were reacted by the tetramethyl benzidine (TMB) method of Mesulam[23] for WGA-HRP visualization. In reacted sections, fluorescent microscopy was first used to collect retrogradely labeled thalamocortical data. Then, anterograde terminal data was collected from the same section using brightfield microscopy. Unreacted sections were used as controls to insure that no diminution of fluorescent label had occurred as a result of the TMB reaction. Data were collected with a microscope stage mounted computerized plotting system (Minnesota Datametrics, Saint Paul, MN) and stored as computer files as described previously[15].

Following data collection, coverslips were removed and sections were stained with cresyl violet and cytoarchitectural boundaries were added to data files. Additionally, alternate sections were stained for cytochrome oxidase (CO)[34] and gold chloride myelin stain[28]. the nissl stain helped distinguish the PO/VPI border based on the larger cell size of PO neurons. The border between VPI and VPL was most easily determined in the CO stained sections based upon the distinctly weak CO staining within VPI. The myelin stain was used to verify borders derived from other stains, however, it also provided information about differences in the locations and patterns of fiber bundles within each lateral thalamic nucleus which will be published in a subsequent report.

The numbers and locations of thalamocortical cells positioned within 100 μm of STT terminals were determined using software developed in our laboratory. These were termed 'overlapped' and were, therefore, considered capable of receiving direct STT input.

RESULTS

Spinal cord injections targeted the dorsal and ventral gray matter from C_5 to T_1, contralateral to the cortical injection sites. Tracer spread throughout the full extent of the cervical enlargement of the hemi spinal cord. These spinal cord injections often included some gray matter on the opposite side, therefore care was taken to avoid spread to high cervical levels (C_1–C_3), to exclude labeling the large number of ipsilaterally projecting STT neurons from this region[1].

Following spinal injections, STT terminals were visualized in regions of the medial and lateral thalamus as described in detail previously[3,15]. In the posterior

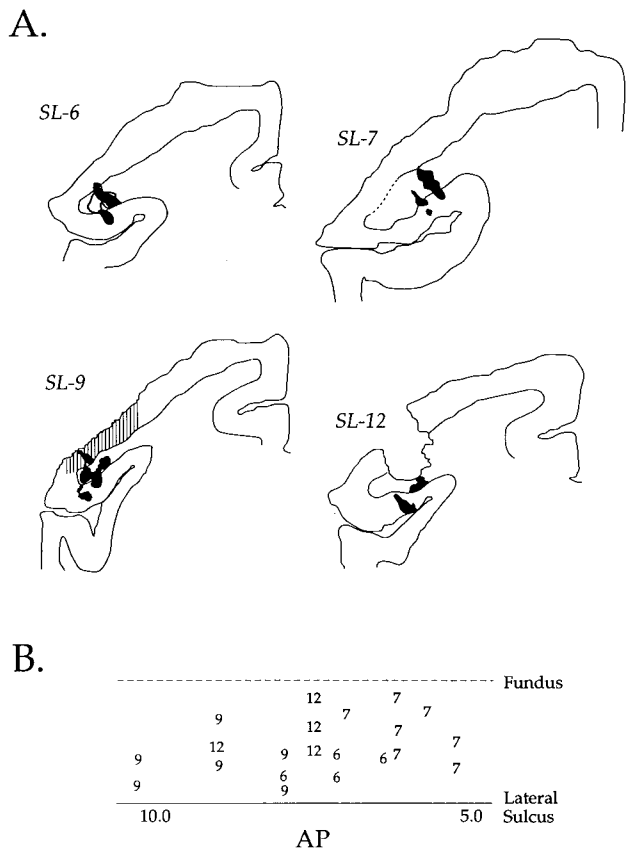

Fig. 1. Diagrammatic representation of SII injection sites in the four squirrel monkeys from which data are presented. A: sample coronal sections from SL-6, SL-9 and SL-12 (diamidino yellow) and SL-7 (rhodamine beads). In two experiments the overlaying SI cortex was intentionally damaged by cauterization (SL-9; cross hatch area) or by suction (SL-12). B: diagram of the surface of the lateral cortex illustrating the numbers and relative positions of pipette penetrations for each experiment. Each number represents one injection track for the experiment of the same number. Anterior is to the left and lateral is down.

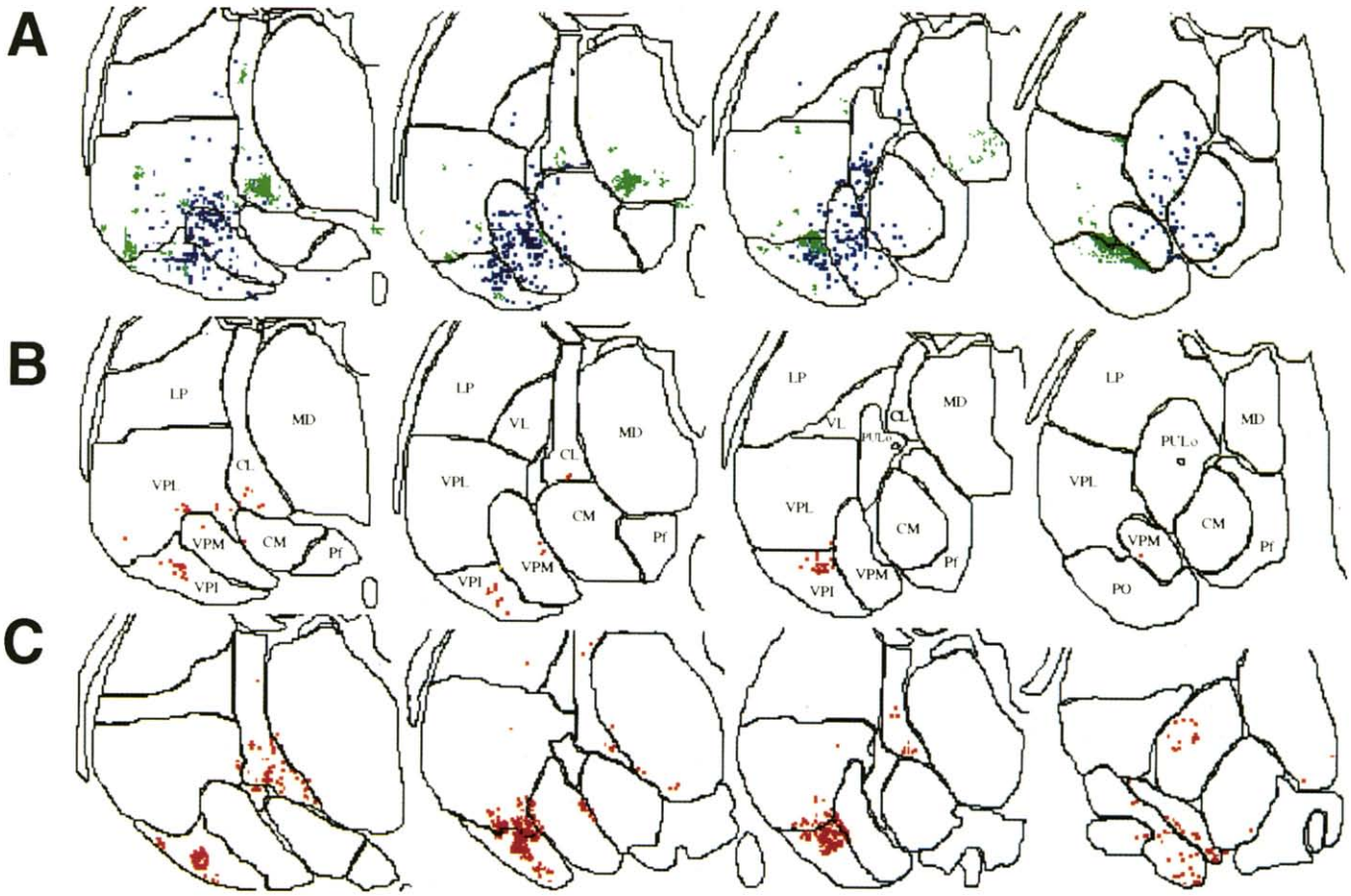

Fig. 2. Sample thalamic plots from four different APs from anterior (left) to posterior (right). A: experiment SL-12. STT terminals (small green dots) from a cervical enlargement injection and SII-projecting cells (large blue dots). B: corresponding section illustrating only thalamocortical cells overlapped within 100 μm of STT terminals (large red dots). C: four plots from experiment SL-7 from approximately equivalent APs illustrating only overlapped SII-projecting cells. CL = centrolateral n.; CM = centromedial n.; LP = lateral posterior n.; MD = mediodorsal n.; Pf = parafascicular n.; PO = posterior n.; PuLo = pulvinar oralis; VL = ventrolateral n.; VPI = ventral posterior inferior n.; VPL = ventroposterior lateral n.; VPM = ventroposterior medial n.

TABLE I

Summary of the distributions of STT-SII overlap cells compared with the previously reported STT-SI overlap distribution

POa = the anterior half of the posterior nuclues

	Number of STT-SII overlap cells / 50 μ section										
	VPI	*VPL*	*POa*	*CL*	*VPM*	*PuLo*	*SM*	*MD*	*CM / Pf*	*OTHER*	*TOTAL*
SL-6	6.9	14	2.5	0.1	0.1	0	0	0	0.1	0	23.7
SL-7	67.1	23.9	32.8	18.4	9	5.7	0.5	1.8	1	1	161.2
SL-9	1.5	0.2	7	5	1.4	1	4.3	0.4	1.2	0	22
SL-12	8.4	1.4	1.5	2	0.9	0	0.4	0.2	0.1	0	14.9
Average	18.9	9.5	10.6	5.9	2.6	1.7	1.2	0.6	0.6	0.3	
Percent	36.4%	18.3%	20.4%	11.4%	5.0%	3.3%	2.3%	1.2%	1.2%	0.6	

	Number of STT-SI overlap cells / 50 μ section										
	VPI	*VPL*	*POa*	*CL*	*VPM*	*PuLo*	*SM*	*MD*	*CM / Pf*	*OTHER*	*TOTAL*
SL-6	25.3	44.5	14.5	9.4	4	4.4	1.8	1.3	0.7	0.8	106.7
Percent	237%	41.8%	13.6%	8.8%	3.7%	4.1%	1.4%	1.2%	0.7%	0.7%	
Gingold *	22.6%	52.3%	5.1% **	10.2%	–	7.9%	–	–	–	1.8%	

* Results previously published for SI by Gingold et al., *J. Comp. Neurol.*, 308 (1991) 467–490.

** Based on entire PO.

thalamus, the most dense region of STT label was in the dorsal and anterior portion of the posterior nucleus (PO; Fig. 2A). More anteriorly, medial label was located primarily in the ventral portion of the mediodorsal (MD) nucleus and intralaminar label was seen throughout the rostrocaudal extent of the centrolateral (CL) nucleus, concentrated in the ventral region. Terminations in the lateral thalamus were located in the ventral border region of VPI and extended dorsally into the forelimb region of VPL in what is commonly described as a 'patchy' or 'archipelago-like' pattern.

The hSII injections were made over an area of 2–6 mm2 and 3.0–4.0 mm deep to the cortical surface. At the injection site, dye often diffused up the electrode tract into the overlaying white matter (Fig. 1A). In initial experiments, it was suspected that the label within VPM resulted from spread of dye to the overlaying face SI. For that reason, in two experiments (SL-9 and SL-12), the overlaying SI region was removed to avoid label from that region. In those experiments, VPM label was little changed from earlier experiments (Table I), implying that the labeled cells in VPM is due to spread of tracer laterally into the face portion of SII. In three experiments the retrograde tracer rhodamine coated latex microspheres (RB) was used within SII while in one experiment (SL-7) diamidino yellow (DY) was used. The latter resulted in the greatest number of labeled SII-projecting cells in the thalamus. Although this increase may be related to a difference in sensitivity of the tracer, this injection was also the largest for these experiments (7 sites) and the most posterior of all injections (Fig. 1B). Therefore, it is unclear to what extent each of these factors affect this increase in thalamic label.

Retrogradely labeled cells from hSII were consistently found within the same thalamic nuclei in all experiments although in variable numbers. Little hSII label was seen in the main body of PO (Fig. 2A). The number of hSII-projecting cells increased in the anterior portion of PO near its junction with VPI. More anteriorly, within VPI most labeled cells were located in the dorsal and medial portion of the nucleus and extended dorsally into the ventral portion of the pulvinar oralis (PuLo) and medially into the lateral portion of the ventroposterior medial nucleus (VPM). In VPL, labeled cells were scattered throughout the ventral portion of the hand region of the nucleus throughout its extent. Additionally, scattered cells were seen in the centrolateral nucleus (CL) concentrated in the ventral-most region.

The lateral thalamus (VPI, VPL and PO) contained large numbers of both STT terminations and hSII-labeled cells, and accordingly, combined to contain over 75% of the overlap cells (Table I). Within the PO nucleus, STT terminals as well as retrograde hSII labeled cells were located only in the anterior portion of the nucleus. For that reason, the numbers of cells per section in PO were calculated only for the anterior half of PO which, for purposes of this report, was termed POa. VPL had a large number of STT-hSII overlapping cells located almost entirely in the ventral portion. The STT-hSII overlapping cells in VPI were variable in position but most often were located either dorsally near the VPL/VPI border, or within the middle portion of VPI, ventral and lateral to non-overlapping hSII-projecting VPI cells. Averaging across all four experiments, VPI had the largest number of STT overlapping cells per section (18.9) followed by POa (10.6) and VPL (9.5). The percentage of SII-projecting cells within VPI, VPL and POa which were overlapped with STT terminals were 22.7%, 22.6% and 30.2% respectively, averaged per 100um section.

More medially within the thalamus, STT terminals were colocalized with hSII-projecting cells within the ventral portions of CL and more sparingly within MD, SM and CM/Pf. Although within CL the numbers of STT-hSII overlap cells/section were quite variable (0.1/section in SL-6 and 18.4/section in SL-7), an average of 11.4% of all identified overlap cells/section were located within CL. In other regions of the thalamus, VPM and PuLo were heavily labeled from hSII injections, however, neither of these thalamic nuclei contained appreciable numbers of STT terminals from cervical enlargement injections and, therefore, demonstrated little overlap.

The distribution of STT-hSII overlapping cells across the thalamic nuclei varied with the portion of SII injected. In SL-9, the anterior-most region of SII was injected (Fig. 1B) and the majority of overlapping cells were found in POa and CL. This injection was the only case which resulted in significant STT-hSII overlapping cells in nucleus submedius. In SL-6, the injections were located in the mid portion of SII antero-posteriorly and restricted to the lateral SII, mediolaterally. In this experiment, VPL was the major source of overlapping cells, and VPI and VPL combined to contribute greater than 88% of the STT-hSII overlap. More medial injections at approximately the same antero-posterior level (SL-12) resulted in overlapping cells primarily in VPI. The most posterior SII injected animal (SL-7) also had the largest number of injections. In this animal, the total number of labeled cells and thus the numbers of STT-hSII overlapping cells were much larger than in the other animals. In SL-7, the distribution of overlapping cells was similar to that in SL-12, with the dominant STT input to hSII being from VPI. The results of

these four experiments suggest that thalamic relay of STT information to SII is differentially distributed to various portions of SII but the major input is from VPI with additional inputs from PO, VPL and CL.

In experiment SL-6, in addition to the RB injection into hSII, the primary somatosensory cortex was injected with 2% FG so that the STT inputs to SI and SII-projecting cells could be directly compared in the same section. Whereas VPI is the main thalamic source of STT information to SII (36.4% of the overlapped cells/section), the VPL had the largest percentage of SI-projecting cells overlapped with STT terminals (41.8% of the STT-hSI cells/section; Table I, bottom). The hSI-STT overlapping cell distribution closely approximates results we have reported earlier [15], averaged over three animals, see Table I.

DISCUSSION

Many lines of evidence have demonstrated a role for the cerebral cortex in nociception. Most of this attention has focused on the primary somatosensory cortex[9,15,18,19]. Kenshalo et al.[19] showed that SI neurons respond to a wide range of nociceptive inputs and Gingold et al.[15] demonstrated that the source of STT nociceptive inputs to the SI cortex is primarily VPL, VPL and CL.

The SII has been shown to play a role in somatosensory integration in monkeys[8,10,17] as well as in human[16]. However, questions remain relating to how somatosensory information accesses the SII region. In cat, evidence suggests a parallel input of somatosensory information from the thalamus to SI and SII since some measure of tactile processing occurs in each region despite removal of the other[6,29]. In the primate, however, it is strongly suggested that tactile information accesses SII serially through SI[7,14,24]. Anatomic data showing dense interconnections between SI and SII support this view[12,25,30].

The current study, however, has demonstrated that SII is capable of receiving STT information directly through connections within thalamic nuclei VPI, VPL and PO. Since it has been previously shown by Gingold et al.[15] as well as in one experiment of the present study (SL-6) that a similar direct spinothalamocortical pathway to SI exists, these results imply that at least a portion of STT (presumably nociceptive) information is distributed in parallel to SI and SII in squirrel monkey. It cannot be determined through these studies to what extent STT information accesses SII by alternate pathways. Additionally, since a large percentage of SII-projecting thalamocortical cells appear not to overlap with STT terminals, it is apparent that other pathways, perhaps multisynaptic spinal pathways, have access to thalamocortical cells projecting to SII.

Despite considerable variability between experiments, VPI demonstrated the highest percentage of overlap between STT terminals and hSII-projecting thalamocortical cells and is likely, therefore, to play a key role in transmitting nociceptive information to hSII. In contrast, the STT inputs to the SI cortex is primarily through VPL with a smaller contribution from VPI and CL[15]. This demonstration of a distinct connectivity between the STT and thalamocortical inputs to hSI and hSII suggests distinct roles in nociceptive processing. This suggestion is supported by electrophysiologic data in squirrel monkey demonstrating a segregation of nociresponsive neuronal types within the lateral thalamus, i.e., the majority of nociceptive specific (NS) units within the thalamus were located in VPI while all nociceptive units in VPL were wide dynamic range (WDR) type[4]. Given the differences between VPI and VPL in their connectivity between STT inputs and projections to SI and SII, as presented here, it is suggested that SI and SII should demonstrate physiologic differences similar to that we have described for VPL and VPI. Therefore, these results predict that within SI, especially in areas 3b and 1 (regions dominated by STT inputs through VPL) all neurons with nociceptive responses should be of wide dynamic type. On the other hand, within SII (where STT inputs are mainly from VPI) both NS and WDR type cells should be observed. Recent physiologic stuctions. Recordings in SI to date have found only WDR type cells, both in the anesthetized[19] and awake monkeys[18] while recent single unit studies in SII of the awake monkey have shown both NS and WDR type neurons[11]. Additionally, since the NS cells comprising the STT are primarily from lamina I neurons of the spinal cord[32] and these lamina I neurons comprise the dorsal spinothalamic pathway[2], it appears that the segregation of the NS and WDR pathways (DSTT and VSTT, respectively) seem to be maintained from the spinal cord, through the thalamus to the cortex.

Although the current study shows that SII is capable of receiving nociceptive information from the STT through VPI, VPL, POa and CL, it is recognized that the method of overlap analysis utilized in this study is a probabilistic estimate of the maximum putative information transfer through terminals, the boutonal endings of which we cannot identify with this methodology. However, the overlap method can become more precise by knowledge of the specific numbers and locations of synapses between STT and thalamocortical cells in different thalamic nuclei. With the latter knowledge, more realistic calculations of the probabili-

ties of contacts can be estimated and compared among pathways, nuclei, and destinations. Such a study is currently underway in our laboratory.

Acknowledgements. This study was partially funded by a grant from the Perkins Foundation.

REFERENCES

1 Apkarian, A.V. and Hodge, C.J., The primate spinothalamic pathways: I. A quantitative study of the cells of origin of the spinothalamic pathway, *J. Comp. Neurol.*, 288 (1989) 447–473.

2 Apkarian, A.V. and Hodge, C.J., The primate spinothalamic pathways: II. The cells of origin of the dorsolateral and ventral spinothalamic pathways, *J. Comp. Neurol.*, 288 (1989) 474–492.

3 Apkarian, A.V. and Hodge, C.J., The primate spinothalamic pathways: III. Thalamic terminations of the dorsolateral and ventral spinothalamic pathways, *J. Comp. Neurol.*, 288 (1989) 493–511.

4 Apkarian, A.V., Shi, T., Stevens, R.T., Kniffki, K-D. and Hodge, C.J., Properties of nociceptive neurons in the lateral thalamus of the squirrel monkey, *Soc. Neurosci. Abstr.*, 17 (1991) 838.(Abstract)

5 Burton, H. and Carlson, M., Second somatic sensory cortical area (SII) in a prosimian primate, Galago crassicaudatus, *J. Comp. Neurol.*, 247 (1986) 200–220.

6 Burton, H. and Robinson, C.J., Responses in the first or second somatosensory cortical area in cats during transient inactivation of the other ipsilateral area with lidocaine hydrochloride, *Somatosens. Res.*, 4 (1987) 215–236.

7 Burton, H., Sathian, K. and Dian-Hua, S., Altered responses to cutaneous stimuli in the second somatosensory cortex following lesions of the postcentral gyrus in infant and juvenile macaques, *J. Comp. Neurol.*, 291 (1990) 395–414.

8 Burton, H. and Sinclair, R.J., Second somatosensory cortical area in macaque monkeys: 2. Neuronal responses to punctate vibrotactile stimulation of glabrous skin on the hand, *Brain Res.*, 538 (1991) 127–135.

9 Chudler, E.H., Anton, F., Dubner, R. and Kenshalo, D.R.,Jr., Responses of nociceptive SI neurons in monkeys and pain sensation in humans elicited by noxious thermal stimulation: effect of interstimulus interval, *J. Neurophysiol.*, 63 (1990) 559–569.

10 Chudler, E.H., Dong, W.K. and Kawakami, Y., Cortical nociceptive responses and behavioral correlates in the monkey, *Brain Res.*, 397 (1986) 47–60.

11 Dong, W.K., Salonen, L.D., Kawakami, Y., Shiwaku, T., Kaukoranta, E.M. and Martin, R.F., Nociceptive responses of trigeminal neurons in SII-7b cortex of awake monkeys, *Brain Res.*, 484 (1989) 314–324.

12 Friedman, D.P., Jones, E.G. and Burton, H., Representation pattern in the second somatic sensory area of the monkey cerebral cortex, *J. Comp. Neurol.*, 192 (1980) 21–41.

13 Friedman, D.P. and Murray, E.A., Thalamic connectivity of the second somatosensory area and neighboring somatosensory fields of the lateral sulcus of the macaque, *J. Comp. Neurol.*, 252 (1986) 348–373.

14 Garraghty, P.E., Pons, T.P. and Kaas, J.H., Ablations of areas 3b (S-I proper) and 3a of somatosensory cortex in marmosets deactivate the second and parietal ventral somatosensory areas, *Somatosens. Motor Res.*, 7 (1990) 125–135.

15 Gingold, S.I., Greenspan, J.D. and Apkarian, A.V., Anatomic evidence of nociceptive inputs to primary somatosensory cortex: relationship between spinothalamic terminals and thalamocortical cells in squirrel monkeys, *J. Comp. Neurol.*, 308 (1991) 467–490.

16 Greenspan, J.D. and Winfield, J.A., Reversible pain and tactile deficits associated with a cerebral tumor compressing the posterior insula and parietal operculum, *Pain*, 50 (1992) 29–39.

17 Horwitz, W. and Ettlinger, G., Unilateral removal of the posterior insula or of area SII: inconsistent effects on tactile, visual and auditory performance in the monkey, *Behav. Brain Res.*, 26 (1987) 1–17.

18 Kenshalo Jr., D.R., Chudler, E.H., Anton, F. and Dubner, R., SI nociceptive neurons participate in the encoding process by which monkeys perceive the intensity of noxious thermal stimulation, *Brain Res.*, 454 (1988) 378–382.

19 Kenshalo, D.R.,Jr. and Isensee, O., Responses of primate SI cortical neurons to noxious stimuli, *J. Neurophysiol.*, 50 (1983) 1479–1496.

20 Krubitzer, L.A. and Kaas, J.H., The somatosensory thalamus of monkeys: cortical connections and a redefinition of nuclei in Marmosets, *J. Comp. Neurol.*, 319 (1992) 123–140.

21 London, S.M. and Apkarian, A.V., Anatomic evidence for a thalamic relay for nociceptive information to secondary somatosensory cortex (SII), *Soc. Neurosci. Abstr.*, 16 (1990) 706.(Abstract)

22 Ma, W., Peschanski, M. and Ralston, H.J.III, The differential synaptic organization of the spinal and lemniscal projections to the ventrobasal complex of the rat thalamus. Evidence for convergence of the two systems upon single thalamic neurons, *Neuroscience*, 22 (1987) 925–934.

23 Mesulam, M-M., Tetramethyl benzidine for horseradish peroxidase neurohistochemistry: a non-carcinogenic blue reaction product with superior sensitivity for visualizing neural afferents and efferents, *J. Histochem. Cytochem.*, 26 (1978) 106–117.

24 Pons, T.P., Garraghty, P.E. and Mishkin, M., Serial and parallel processing of tactual information in somatosensory cortex of rhesus monkeys, *J. Neurophysiol.*, 68 (1992) 518–527.

25 Pons, T.P. and Kaas, J.H., Corticocortical connections of area 2 of somatosensory cortex in macaque monkeys: a correlative anatomical and electrophysiological study, *J. Comp. Neurol.*, 248 (1986) 313–335.

26 Ralston, H.J., Peschanski, M. and Ralston, D.D., Fine structure of spinothalamic tract axons and terminals in rat, cat, and monkey demonstrated by the orthograde transport of lectin conjugated to horseradish peroxidase. In H.L. Fields, R. Dubner and F. Cervero (Eds.) *Advances in Pain Research and Therapy*, Raven Press, New York, 1985, pp. 269–275.

27 Ralston III, H.J., Synaptic organization of spinothalamic tract projections to the thalamus, with special reference to pain. In L. Kruger and J.C. Liebeskind (Eds.) *Advances in Pain Research and Therapy*, Raven Press, New York, 1984, pp. 183–195.

28 Schmued, L.C., A rapid, sensitive histochemical stain for myelin in frozen brain sections, *J. Histochem. Cytochem.*, 38 (1990) 717–720.

29 Schwark, H.D., Esteky, H. and Jones, E.G., Corticocortical connections of cat primary somatosensory cortex, *Exp. Brain Res.*, 91 (1992) 425–434.

30 Weller, R.E., Sur, M. and Kaas, J.H., Callosal and ipsilateral cortical connections of the body surface representations in SI and SII of tree shrews, *Somatosens. Res.*, 5 (1987) 107–133.

31 Whitsel, B.L., Petrucelli, L.M. and Werner, G., Symmetry and connectivity in the map of the body surface in somatosensory area II of primates, *J. Neurophysiol.*, 32 (1969) 170–183.

32 Willis, W.D., Trevino, D.L., Coulter, J.D. and Maunz, R.A., Responses of primate spinothalamic tract neurons to natural stimulation of hindlimb, *J. Neurophysiol.*, 37 (1974) 358–370.

33 Willis, W.D.,Jr. and Coggeshall, R.E., Sensory pathways in the dorsal funiculus. In *Sensory Mechanisms of the Spinal Cord*, Plenum Press, New York, 1991, pp. 245–306.

34 Wong-Riley, M., Changes in the visual system of monocularly sutured or enucleated cats demonstrable with cytochrome oxidase histochemistry, *Brain Res.*, 171 (1979) 11–28.