Proprioceptive and Cutaneous Representations in the Rat Ventral Posterolateral Thalamus

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[1]*Department of Physiology and Pharmacology,* [2]*Program in Neural and Behavioral Science, and* [3]*Program in Biomedical Engineering, State University of New York Downstate Medical Center, Brooklyn, New York*

Francis JT, Xu S, Chapin JK. Proprioceptive and cutaneous representations in the rat ventral posterolateral thalamus. *J Neurophysiol* 99: 2291–2304, 2008. First published February 20, 2008; doi:10.1152/jn.01206.2007. Determining how and where proprioceptive information is represented in the rat ventral posterolateral (VPL) is important in allowing us to further investigate how this sense is utilized during motor control and learning. Here we demonstrate using electrophysiological techniques that the rostral portion of the rat VPL nucleus (rVPL, -2 to -2.5 mm bregma) carries a large amount of proprioceptive information. Caudal to this region is a zone where the cutaneous receptive fields are focal (mVPL for middle VPL, -2.5 to -3.2 mm bregma) with a fine topographic map of the fore- and hindlimbs. The forepaw is represented with digit 1 medial and each subsequent digit increasingly lateral, all of which are dorsal to the pads. The caudal VPL (cVPL, -3.2 to -4.0 mm bregma) has broad receptive fields and is the target of lamina 1 and lamina 2, as well as the dorsal column nuclei, and may represent the flow of nociceptive information through the VPL. Thus we propose that the VPL may be thought of as three subnuclei—the rostral, middle, and caudal VPL— each carrying preferentially a different modality of information. This pattern of information flow through the rat VPL is similar, although apparently rotated, to that of many primates, indicating that these regions in the rat (rVPL, mVPL, and cVPL) have become further differentiated in primates where they are seen as separate nuclei (VPS, VPL, and VPI/VMpo).

INTRODUCTION

Sensory feedback is essential for an animal to control its own movements. Both vision and proprioception are considered to be important for motor learning and performance in human and nonhuman primates (Ghez and Sainburg 1995; Gordon et al. 1995; Graziano 1999; Saunders and Knill 2003). However, many animals including rodents have their eyes situated such that they provide little information about limb positions. Thus it is plausible that such animals depend more heavily on proprioception, tactile, and other sensory modalities while moving their limbs during locomotion or while manipulating food items (Ballermann et al. 2001; Doetsch et al. 1988; Whishaw and Tomie 1989). Surprisingly little is known about the processing of proprioceptive information within the rat ventral posterolateral (VPL) thalamus, and there has been some debate among researchers in the past as to the topography of the cutaneous representation within this nucleus. Earlier work by a host of researchers describing either the electrophysiolog-

ical response properties (Angel and Clarke 1975; Davidson 1965; Emmers 1965) or thalamocortical connections (Fabri and Burton 1991) of the rat VPL delineated the general cutaneous topographic representation (Price 1995; Tracey and Waite 1995). Results from these researchers have differed to some degree, indicating the need for further study. It has been shown that projections from lamina I and lamina II of the rat spinal cord at the level of C7 project to the caudal portion of the VPL (Gauriau and Bernard 2004). Lund and Webster have described two pathways from the spinal cord to the VP (ventroposterior nucleus, comprised of VPM and VPL), with one projecting to the caudal portion and the other to the rostral portion of the VP (Lund and Webster 1967a,b). They suggested that the middle portion of the VP received most of its projections from the dorsal column nuclei. Based on electrophysiological experimentation Emmers (1965) suggested that the caudal portion of the VP had responses that were less focal and bilateral compared with the rostral portion that had contralateral focal receptive fields. He named these regions S2 and S1, respectively. This segregation of pathways into the VP and differences in response properties suggest that the VP is modular and may be divided into subnuclei. In the work presented here we have used electrophysiological techniques to map out neural responses in the VPL to both cutaneous and proprioceptive peripheral stimulation. Here we present results from this work and discuss the relation between the rat VPL and other mammalian species.

METHODS

Animal preparation

All animal procedures were approved by SUNY Downstate Medical Center IACUC and conformed to National Institutes of Health guidelines. Female Long–Evans rats (Charles River Laboratories, Wilmington, MA), weighing between 250 and 450 g, were anesthetized with isoflurane in preparation for an intraperitoneal injection of pentobarbital (50 mg/kg), at which time administration of isoflurane was stopped. Atropine sulfate (0.05 mg/kg, intramuscular) was administered to reduce bronchial secretions. In addition we administered dexamethasone (0.1 mg/kg) to prevent swelling of the brain. Once a surgical level of anesthesia was obtained, as determined by the lack of any withdrawal reflex to a painful foot pinch, the rat was mounted onto a stereotaxic device (Kopf Instruments, Tujunga, CA). Supplemental injections of pentobarbital (1/4 to 1/3 of initial dosage) were given as needed. As a further precaution an isoflurane system was used to keep the animal at a surgical level of anesthesia in case the

animal became too light, at which time we administered more pentobarbital. Once the animal's level of anesthesia was secure the isoflurane was discontinued. The animal was placed on a heating pad that was kept at or near 38°C. We did not notice any changes in the stability of the animal preparation over the course of a typical experiment, which was about 5–8 h. A craniotomy was performed at the left hemisphere, exposing a portion of the cortex starting at bregma and extending caudally 5 mm. The mediolateral extent was about 4.5 mm starting at the midline. The bregma and lambda positions were measured and the animal's snout positioned such that the two landmarks lay in the same plane parallel to the surface of the stereotaxic floor. This arrangement is the same as that used in the Paxinos and Watson (1998) atlas. After this initial study was conducted and our somatotopic mapping of the VPL was complete we conducted five more experiments, using urethane (1.2 g/kg) as the main anesthetic, testing the accuracy of our maps. A second aim of these latter experiments was to make electrolytic lesions in separate VPL regions and obtain histology for comparison.

Multiple penetrations were made during each experiment using either a single tungsten electrode (impedance 10 MΩ) or a concentric bipolar electrode (impedance 5 MΩ; FHC, Bowdoinham, ME). The electrode was maneuvered using a micromanipulator (Kopf Instruments). The signal was passed from the electrode to a ×1,000 amplifier with band-pass filtering from 100 Hz to 9 kHz (MAP system; Plexon, Dallas, TX). This signal was passed to an oscilloscope and an audio amplifier that allowed us to hear and see the multiunit responses to cutaneous and proprioceptive stimulation. We explored an area of the thalamus extending from −1.8 to −4 mm rostrocaudally and 1.8 to 4.0 mm mediolaterally. At the end of each experiment animals were killed with isoflurane gas, except for the five rats used for histological purposes (see description under *Histology*).

Proprioceptive mapping

In an effort to keep cutaneous stimulation to a minimum we removed the hairy skin from the right forelimb extending from above the shoulder down to the wrist ($n = 14$). The skin was removed only after a preliminary cutaneous mapping of the forearm region. The skin of the hand was left intact and cutaneous stimulation of it aided in determining our electrode position in the VPL based on our cutaneous mapping (see following text). Once the paw's receptive field was obtained and putative proprioceptive activity found, the hand was injected with copious amounts of lidocaine, which fully extinguished neural responses due to cutaneous stimulation of the paw. We found that this level of local anesthesia required injecting the hand in several sites on the dorsal, lateral, and ventral sides.

Both mechanical and electrical stimulation were used in determining the receptive fields of muscles and joints. First, palpation was used to determine the general areas that produced neural responses. If the neural activity appeared to be in response to muscle receptors then a moist cotton swab was used to apply light, moderate, or deep pressure and tapping in an attempt to elucidate the individual muscles that made up the receptive field. It was often helpful to stretch and relax the muscles by manipulating the joints to determine whether the receptive field became more sensitive while the muscle was stretched than when it was relaxed, as would be expected if the neural activity were due to muscle spindles. It is important to note that we do not seek to make claims about the types of receptors that produced the activity, but rather describe the types of stimuli that caused the response. While mapping the muscles and joints via palpation and manipulation it was important to isolate pressure and movement to the joint or muscle that we were testing because movement of a joint affects a large number of muscles that in turn act on other joints. Therefore we often used forceps to fix one joint while working on the muscles distal to it. We found it very difficult to isolate the receptive field to individual muscles with the muscles attached and therefore describe our results on the basis of general locations such as dorsal forearm rather than

specifying individual muscles so as not to overstate our accuracy in this regard. During these experiments the muscles were kept moist by periodically applying warm Ringer solution.

Cutaneous mapping

During our cutaneous mapping we used similar types of stimuli that others have used in the past such as light touch that just moves the hairs of the fur, touch that is strong enough to elicit skin receptors without causing muscle stimulation, and deep palpations strong enough to stimulate muscle spindles. We also manipulated the joints during these experiments to supplement our proprioceptive mapping. In our early experiments ($n = 7$) we sampled a large area of the thalamus to obtain a general map of the entire body representation with no bias. Subsequently, we concentrated on areas of the thalamus that contained the forelimb representation. During these later experiments we still collected a great deal of information on the hindlimb as well as the body representation, which is reflected in RESULTS.

In an effort to briefly describe neuronal latencies we used an electrically driven (1 Hz) mechanical stimulator (MFE R4-155) to elicit responses within a neuron's receptive field. This stimulator produced a tapping motion that was applied to the skin via a wooden shaft. A precision timer supplied a timing pulse for both the mechanical stimulator as well as to our recording system (MAP system, Plexon), which allowed us to easily produce peristimulus time histograms (PSTHs) using Nex software (Nex Technologies, Dallas, TX).

Histology

In a subset of five experiments we made electrolytic lesions along our electrode tracks; specifically, we marked the border of the VPL, that is we made lesions when we first encountered the VPL and when we were leaving it as determined via our electrophysiological mapping of receptive fields guided by our stereotaxic measures and an atlas of the rat brain (Paxinos and Watson 1998). Electrolytic lesions were made by passing 15 μA of current using monopolar stimulation with a biphasic square-wave input (20 s each phase). After the mapping experiment was complete these five animals were killed with an overdose of pentobarbital (100 mg/kg) and then perfused transcardially with 0.5 L of Ringer solution followed by 0.5 L of 4% paraformaldehyde. The brains were removed and stored in cold 4% paraformaldehyde for ≥1 wk. The formalin-fixed brains were placed in frozen tissue-embedding media (SH75-125D, Fisher Scientific) and frozen with liquid nitrogen overnight. The frozen brains were then blocked in the desired orientation and cut into 60-μm sections with a microtome. These sections were mounted on slides, dried, and stained with cresyl violet stain.

RESULTS

We made a total of 327 penetrations in the left hemisphere from 35 female Long–Evans rats with an average age of 5.61 mo, weight of 319 g, and lambda–bregma distance of 8.77 mm. In 14 experiments we removed the skin from the right forearm and concentrated on proprioception with a total of 137 penetrations. In the remaining 21 experiments we mapped primarily the cutaneous receptive fields on the forepaw, but gathered data on the whole body as well as on proprioception of the intact forelimb with a total of 190 penetrations.

Cutaneous receptive field size varies along the rostrocaudal axis

We found that the size of the receptive fields (RFs) changed substantially as one moves along the rostrocaudal axis of the VPL. It should be noted that this difference in RF size is most

obvious when looking at the fore- and hindpaws because the RFs on the body and limbs are generally broad. Neurons within the rostral and caudal VPL regions (rVPL and cVPL, respectively) usually have large diffuse RFs. Typical RFs in these areas include several digits, the whole palm, or even the whole paw. In contrast, RFs in the middle portion (mVPL) have small and focal RFs. Typical RFs in this area are restricted to a single digit, a single palmar pad, or an individual digit segment.

In Fig. 1 we have shaded typical RFs found on the forepaw from the three VPL regions (gray area, Fig. 1, *D–F*), as well as PSTHs centered on an approximately 1-Hz mechanical stimulus at the center of the RF (see METHODS). Each *inset* in Fig. 1 depicts the location of the neuron in the horizontal plane with the distance in millimeters from bregma, lateral to the midline, and depth from the pial surface. These three cells had approximately the same response latency of 7 ms. We did not test the

latencies of most neurons and thus do not wish to make any claims as to the probabilities of cellular latencies within the three VPL regions, but rather that one can find cells in each of the three VPL regions with short latencies. Each cell in Fig. 1 was taken from one experiment where several cells from each region were found to have similar short latencies. Thus both cells with small and large receptive fields can have the same short latency contrary to the results reported by Angel and Clarke (1975).

Results from an experiment in which we concentrated our electrode penetrations along a sagittal plane about 2.8 mm from the midline are represented in Fig. 2. Receptive fields on the body are represented by solid squares, with the forelimb represented by solid circles and the hindlimb by solid triangles. One can see from this figure that there is a shift in the RF size and modality as one travels along the rostrocaudal axis, which is represented by the three differentially shaded regions. At this lateral extent the rVPL is carrying mostly proprioceptive information from the hindlimb, as can be seen from the RFs encountered in our rostral-most electrode penetration (see Fig. 2). The first RF is to ankle extension as is indicated by the bold arrow, where arrows indicate the direction of movement of the nearest joint that increased the neural response. The capital (T) indicates that the neural response was tonic. We found a large number of RFs in the rVPL that responded in a tonic fashion compared with the mVPL. Notice that the RFs in the mVPL region are focal and in this sagittal plane represent the forepaw. Moving to the cVPL the RFs once again become large as they were in the rVPL, although in the cVPL, they are cutaneous in nature.

Trends in cutaneous RFs of the mVPL

In Fig. 3 we describe the results from a typical experiment mapping the mVPL (−2.7 mm from bregma). On the left side of this figure we have plotted information regarding the location of six electrode tracks with the positions at which data were obtained. Positions where forepaw RFs were found are marked with a filled circle and are labeled with numbers corresponding to their RFs seen within the drawing of the mVPL. Filled circles without a number have a similar RF to the region numbered above it in the same electrode path. Thus we can see in Fig. 3 that the most medial penetration has an RF on the vestigial digit 1 for the first three electrode positions within the mVPL. Subsequently, as one goes deeper the RF moves to the pad adjacent to digit 1.

Several trends can be seen in Fig. 3. First, as one moves from the medial to the lateral mVPL the RFs move in the same manner, that is from the digit 1 (medial) side of the paw to digit 5 (lateral) side. The second clear trend is that as one goes deeper within the thalamus the RFs move from the digits to the pads. We found that the claws have a strong representation, as do the hairs that cover the claws represented by RF 7 in Fig. 3. In the mVPL we generally found that as we moved from the surface of the cortex through the mVPL RFs first appear on the whiskers (VPM), second on the jaw, and then either suddenly the RFs jumped to the forepaw, or in more lateral portions of the mVPL we first encountered a brief period of forelimb before it jumped to the hindlimb, as can be seen in Fig. 3 (RFs 21–24) and our summary in Fig. 6*B*. It is clear from Figs. 2, 3, 6, and 7 that the surfaces used for tactile exploration are more
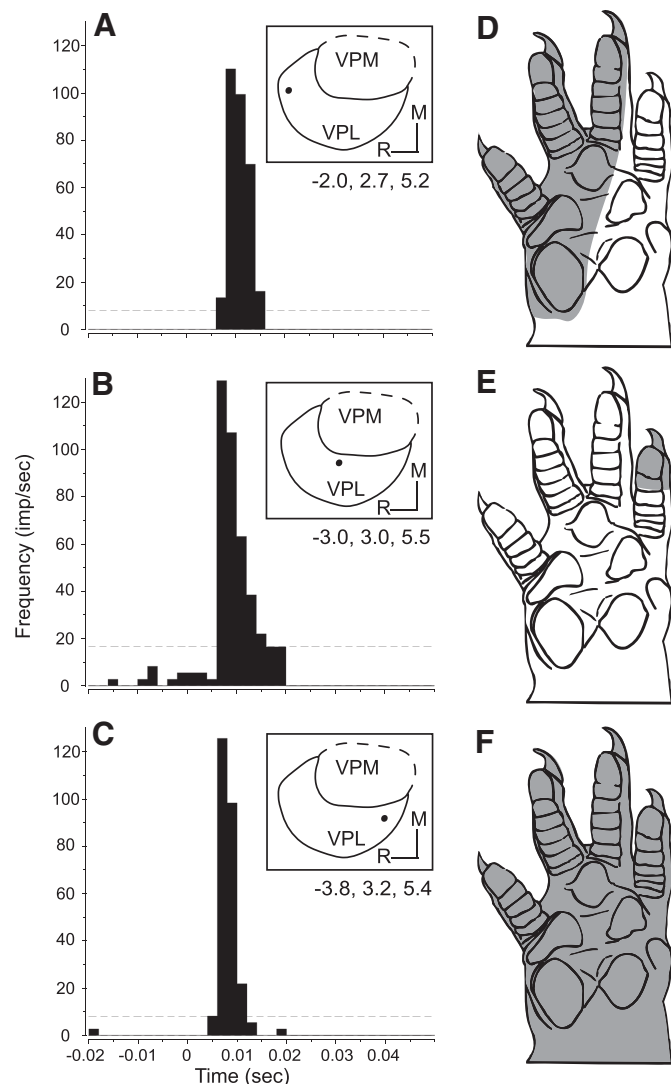

FIG. 1. The size of receptive fields at different ventral posterolateral (VPL) regions. Peristimulus time histograms (PSTHs) (*A–C*) and corresponding receptive fields (*D–F*) for 3 neurons recorded in rostral (*A, D*), middle (*B, E*), and caudal (*C, F*) VPL. Each PSTH is centered on a mechanical stimulation delivered at 1 Hz (see METHODS). The recording electrode position is shown in a horizontal plane of VP (*inset*); the coordinates for each cell with respect to bregma, lateral displacement from the midline, and depth from the pial surface (in millimeters) are recorded below the *inset*. M, medial; R, rostral.
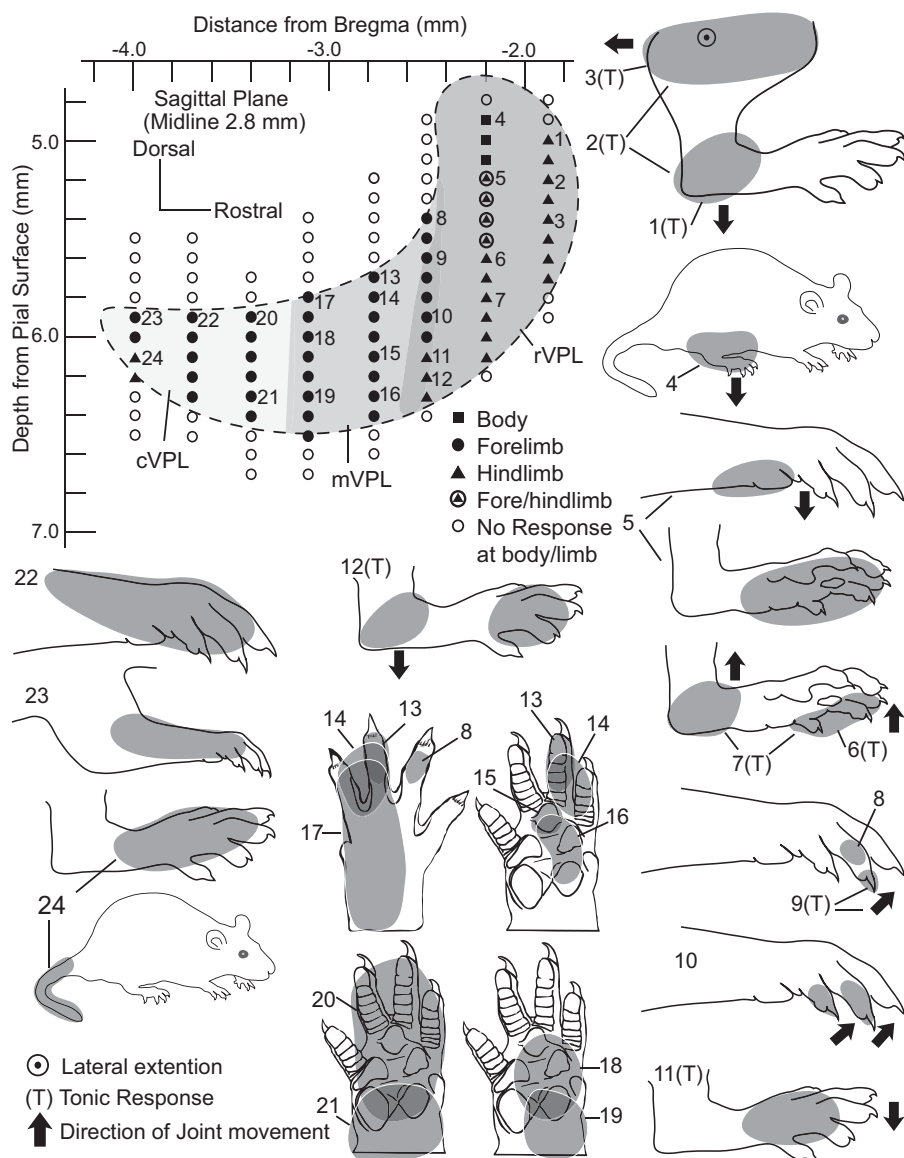
FIG. 2. Results from a typical experiment on the sagittal plane 2.8 mm from the midline. Coordinate map on the *top left* depicts the positions where data were taken, with different symbols standing for receptive field (RF) regions on the body. The approximate partitions of rostral (rVPL), middle (mVPL), and caudal (cVPL) VPL regions are indicated by 3 shaded areas: dark gray, gray, and light gray, respectively. Each area grouped RFs of similar response characteristics. Numbers represent RFs depicted in the figure. Filled symbols without a number have a similar RF as the numbered symbols above them. The boundary of VPL is depicted with the dashed line. The movement direction of joints is indicated by adjacent symbols (i.e., arrows, etc.; see key).

heavily represented than areas such as the dorsal surface of the paw. It should be noted that the guard hairs are also well represented, and cellular responses to the slightest movement of these two hairs caused impressive neural responses as if one was moving a whisker. It is possible that rats use these guard hairs as whiskers for the forelimb.

Mapping the sagittal plane (Fig. 2) revealed additional RF trends in the mVPL. First, in the dorsoventral aspect, we still encountered the digits first then the palmar pads (RFs 13 to 16 in Fig. 2). Second, in the rostrocaudal aspect, lateral digits were represented in a more rostral portion of mVPL (RF 8 vs. RF 13 in Fig. 2). The fact that lateral digits are represented more rostrally in the sagittal plane of Fig. 2, whereas in the coronal plane the representation maintains a digit 1 to digit 5 arrangement in the mediolateral axis, indicates the forepaw representation follows the VPL curvature (Fig. 7A).

Proprioception and the rVPL

The rostral portion of the VPL (rVPL, about −2.0 to −2.5 mm from bregma) is responsive to both cutaneous and propri-

oceptive stimulation. In general, the receptive fields on the forepaw appear broad and are often associated with movement of the digit joints. Of course as one moves the digit joints, the muscles and tendons of the forearm and paw are moved as well. We have found a disproportionately large forearm representation in the rVPL compared with the upper arm. Thus the triceps, biceps, and muscles of the shoulder have a smaller representation than the forearm muscles, which may be due simply to the fact that there are more muscles in the forearm.

Figures 4 and 5 represent data taken from a typical experiment mapping the rVPL. In this experiment we have removed the skin of the forearm and have filled the forepaw with lidocaine (see METHODS) to limit any cutaneous activity. It should be noted that we found similar results with the intact forelimb; thus any thalamic reorganization that may have occurred due to the change in sensory input was not substantial enough to change the general patterns we subsequently describe. Filled circles in Figs. 4 and 5 represent positions where we obtained RFs on the forelimb, filled triangles areas where the RFs were on the hindlimb, and filled squares RFs on
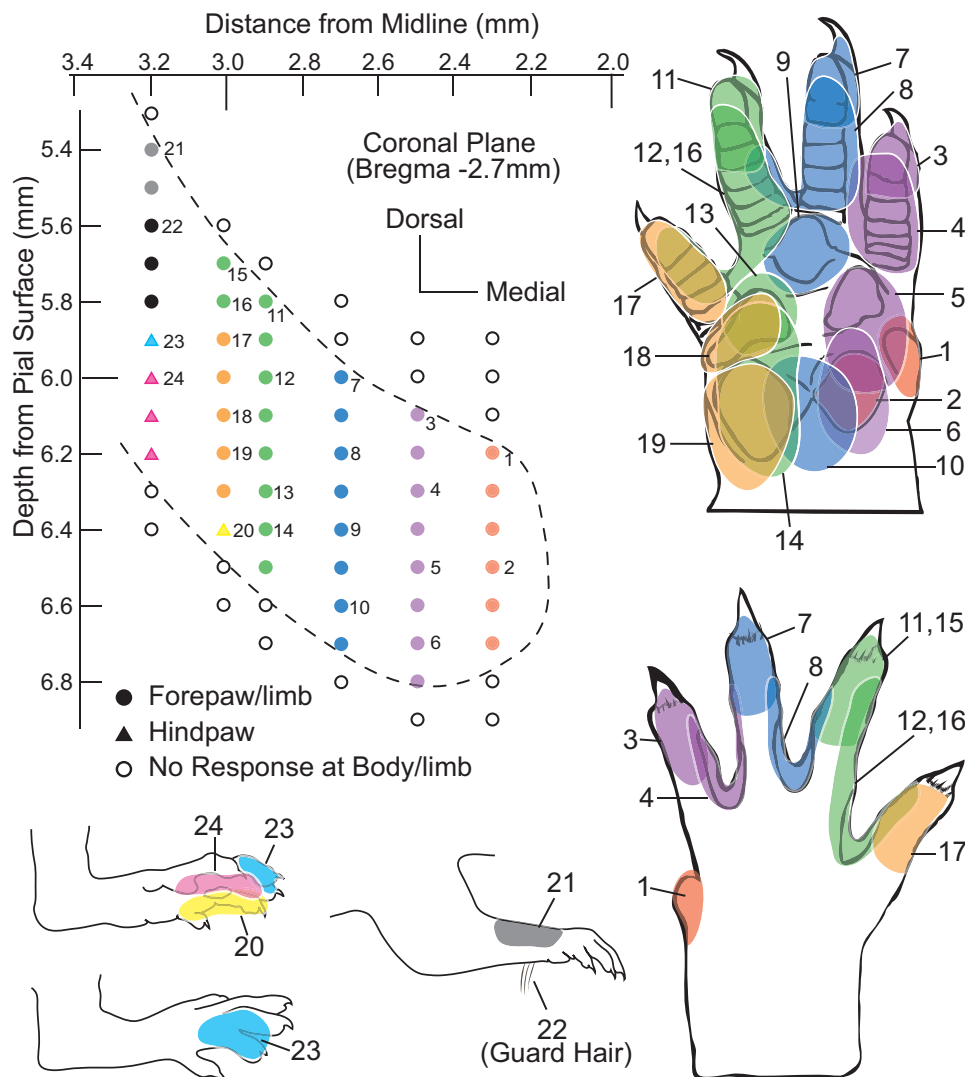
FIG. 3. Results from a typical mapping experiment of the middle VPL (−2.7 mm from bregma). Coordinate map in the *top left* depicts the positions where data were taken, with different symbols standing for RF regions on the body. Numbers represent RFs depicted in the figure. RFs and their corresponding symbols are color-coded to better visualize the multiple overlapping of adjacent fields. Filled symbols without a number have a similar RF as the numbered symbols above them. The boundary of VPL is depicted with the dashed line.

the body. The positions of each point are given in the mediolateral direction as well as the depth from the pial surface. These coronal planes were approximately −2.3 mm from bregma for Fig. 4 and −2.5 mm for Fig. 5. Because there was no skin on the forearm these RFs are proprioceptive in nature. All arrows indicate movement of the closest joint in the direction that caused neural activity. Curved arrows indicate that the RF was turning to the respective joint in the direction indicated. Thus we can see in our most medial penetration in Fig. 4 an RF is to much of the dorsal forelimb. In all descriptions we assume the rat to be in a position such that it is lying down with the forelimbs out to the side, palm surface facing down. This first RF also included elbow extension as is indicated by the bold arrow pointing down. In the second most medial penetration the second RF (3) is to electrical stimulation of the biceps indicated by an "E". This RF also included mechanical stimulation to the shoulder and dorsal forelimb as well as to elbow flexion. As we moved the electrode deeper the RF included turning the paw either counterclockwise or clockwise. We use similar conventions in both Figs. 4 and 5, as the keys on each figure describe.

In our most medial penetration in Fig. 5 we first hit the upper arm representation and found RFs to turning the shoulder joint

away from the head as is represented by the curved arrow. The cells encountered in this penetration also responded to extending the elbow, as well as to lifting the arm up (in the direction out of the page: ⊙) so as to stretch the pectorals. The shaded areas seen in Figs. 4 and 5 represent RFs to mechanical stimulation (M) unless otherwise specified by an E (electrical stimulation), where the electrical stimulation was just sufficient to cause a small muscle contraction. These figures demonstrate that generally the RFs in this area were to several muscles and joints. The finding that the muscle receptive fields are not in an obvious somatotopic organization, other than the general trend of the forelimb being medial to the hindlimb, is similar to that found in the cortical proprioceptive representation (Gioanni 1987). Receptive fields for the wrist and forearm are heavily overlapped, as one would expect, because movement of the wrist causes the attached forearm muscles to stretch or contract leading to muscle spindle activation. We found cells that appeared to encode position of the wrist as they responded in a tonic fashion with an increase in frequency as the wrist was pushed in one direction and decreased their activity in the opposing direction. There were a larger number of RFs that responded to fast movements of the wrist while still indicating direction because they would respond to fast movements of the
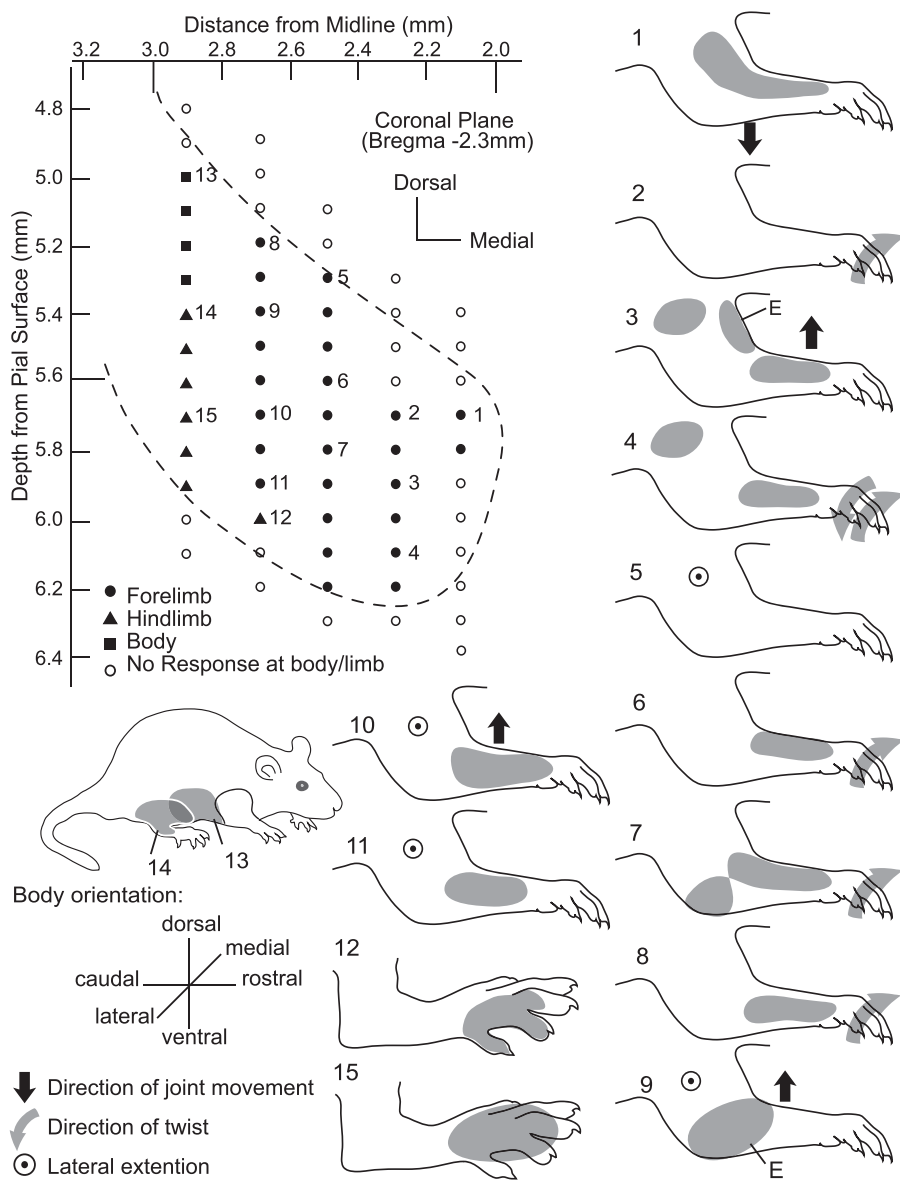
FIG. 4. Results from a typical mapping experiment of the rostral VPL (−2.3 mm from bregma; skin was removed from forelimb and the forepaw was injected with lidocaine). Coordinate map on the *top left* depicts the positions where data were taken, with different symbols standing for RF regions on the body. Numbers represent RFs depicted on the *bottom right* of the figure. Filled symbols without a number have a similar RF as the numbered symbols above them. The boundary of VPL is depicted with a dashed line. The shaded areas depict the mechanical touch unless indicted with an "E" (electrical stimulation). The movement direction of joints is indicated by adjacent symbols (i.e., arrows, etc.; see the keys in the figure).

wrist in only one direction. Such RFs were also found in abundance for the elbow joint and, to a lesser extent, for the shoulder. To further determine whether there is a musculotopy in the rat VPL it will be necessary to detach individual muscles and determine the RFs in such a preparation. It should be noted that many of the unfilled circles seen in Fig. 5 within the boundary of the VPL most certainly had receptive fields on the forepaw, which has been injected with lidocaine, or represent cutaneous portions of the forelimb skin that has been removed. Note that the number of such unfilled circles is greater at the level of −2.5 mm from bregma compared with −2.3 mm from bregma, indicating the transition into the cutaneous mVPL.

Summary of the VPL somatotopy

Figures 6 and 7 provide an overview of our results taken from all 35 experiments including 327 penetrations. In Fig. 6*A* we have a summery of the rVPL results indicating the major trends we found with the body represented in the dorsolateral portion of the rVPL with the hindlimb and hindpaw situated below it. Medial to the hindlimb is the forelimb and forepaw. Because we did not find a reproducible musculotopy beyond the major trends presented earlier in Figs. 4 and 5, we have simply labeled the regions where the different limbs are represented. The representation of the forepaw digits occupies an island of rVPL located in the mediodorsal rVPL surrounded by the forelimb muscles.

Figure 6*B* depicts the average somatotopy from the mVPL presented in the coronal plane at the level of −2.7 mm from bregma. All of the trends previously mentioned for the mVPL can be seen clearly in this figure. In addition, one can see the general representation of the hindlimb as well as the body and tail. Notice that the forepaw and hindpaw have disproportionately large representations compared with the rest of the respective limbs, with the digits represented dorsal to the pads in both the fore- and hindpaws. The representation of the hindpaw is similar to that of the forepaw in that digit 1 is medial with subsequently more lateral digits situated increasingly lateral
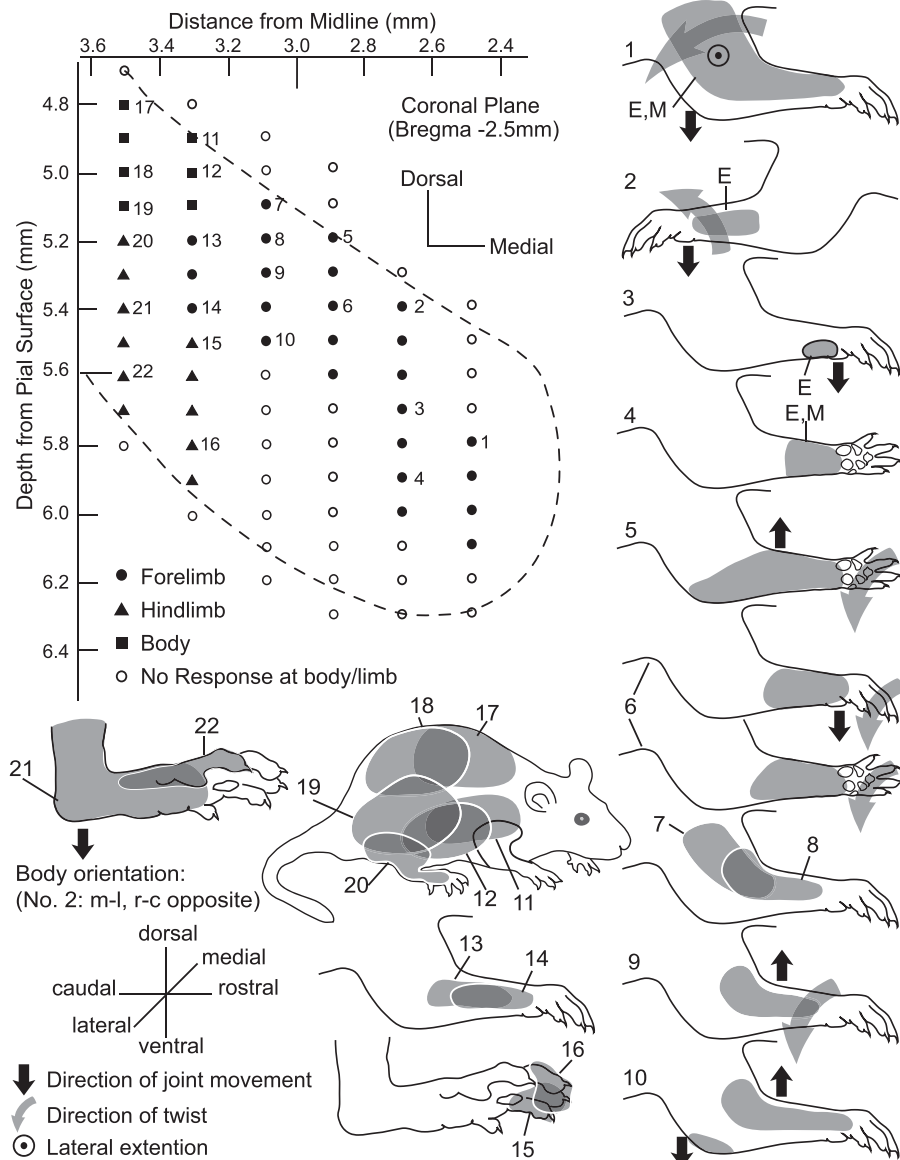
FIG. 5. Results from a typical mapping experiment of the rostral VPL (−2.5 mm from bregma; skin was removed from forelimb and the forepaw was injected with lidocaine). Coordinate map on the *top left* depicts the positions where data were taken, with different symbols standing for RF regions in the body. Numbers represent RFs depicted on the *bottom right* of the figure. Filled symbols without a number have a similar RF as the numbered symbols above them. The boundary of VPL is depicted with the dashed line. The shaded areas depict the mechanical touch unless indicted with an "E" (electrical stimulation). The movement direction of joints is indicated by adjacent symbols (i.e., arrows, etc.; see the keys in the figure).

within the mVPL, although the hindpaw representation appears to be smaller than that of the forepaw.

In Fig. 7A we describe the VPL at the horizontal level of −6.0 mm from pial surface. At this depth most of the VPL carries information on the fore- and hindpaws. The digits of the forepaw follow the curvature of the VPL while keeping their mediolateral organization. Due to this curvature one can imagine the order of RFs in the sagittal plane may jump from one digit to a more medial one as one goes further from bregma; this can be seen in Fig. 7B, which represents the somatotopy of the VPL displayed in a sagittal plane 2.8 mm from the midline.

After we completed making the map seen in Figs. 6 and 7 we conducted another set of experiments to test our map as well as to make electrolytic lesions in the different VPL subnuclei and to collect histological sections of these regions. In Fig. 8 we have two typical examples of the VPL in the sagittal (A–B) and coronal (C–D) planes. We have made lesions at the border of the VPL; that is, we made our first lesion in each electrode track when we found the first somatosensory receptive field on the body, limbs, or paws. This was often marked by a clear

transition of receptive fields from whiskers to lower jaw and finally to limbs, as the electrode traveled from VPM to VPL. We made a second lesion in each track as we were leaving the VPL, which was evident as the neural responses, RFs, would become quieter and less robust and finally disappear. The RFs were as expected given the maps in Figs. 6 and 7. Based on our electrophysiological recordings and lesions we have drawn in the approximate borders of the VPM and VPL. We did not find any obvious differences between the VPL regions using cresyl violet stain, although this was not a focus of this work. Further histological analysis will be needed to determine whether these different VPL regions (rVPL, mVPL, and cVPL) have obvious histological distinctions and borders.

DISCUSSION

We have determined that the ventral posterior lateral thalamic nucleus of the rat may be subdivided into three subnuclei based on electrophysiological responses from these regions. We have designated these three regions the rostral (rVPL),
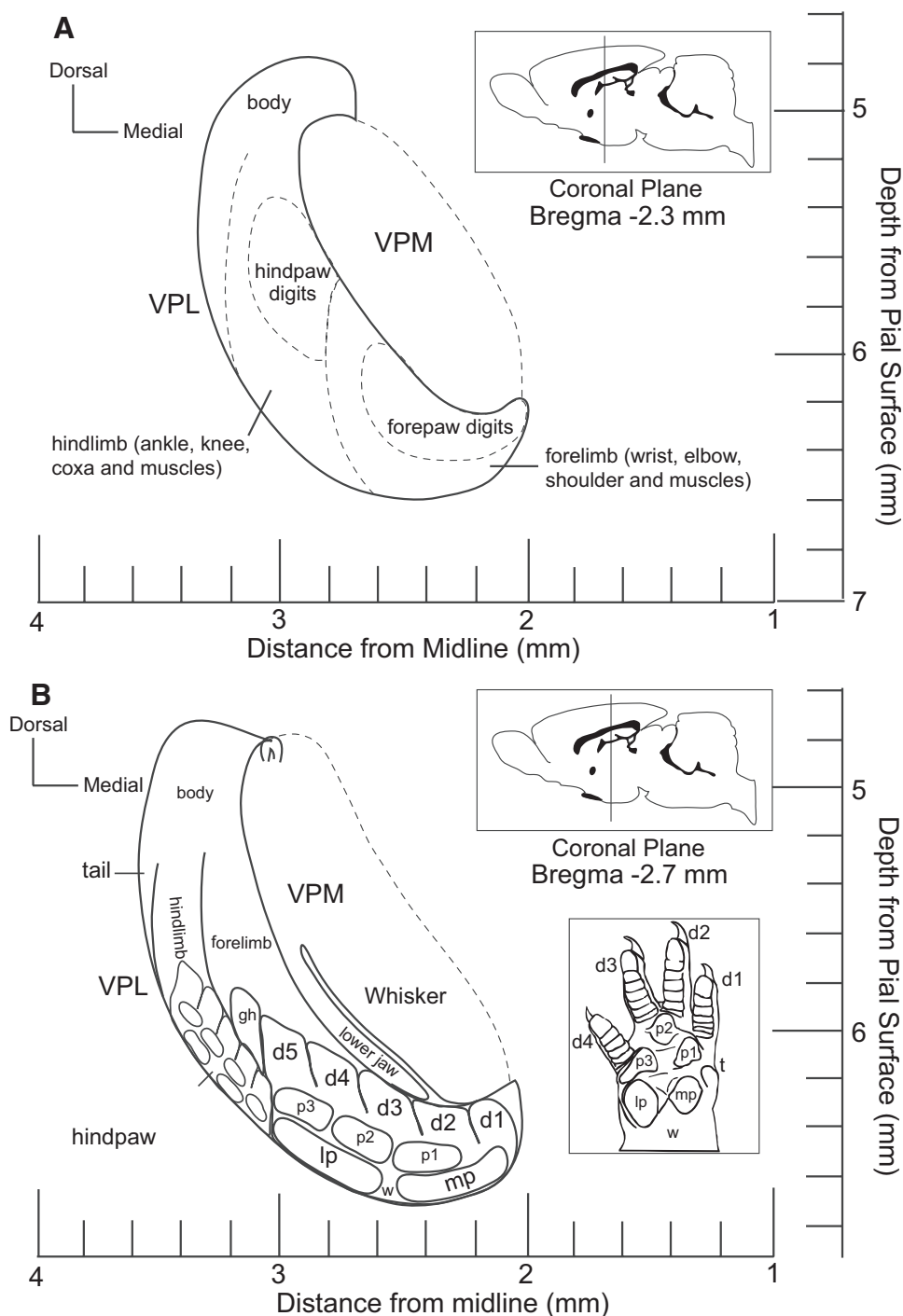
FIG. 6. Schematic drawing of somatotopy in the VPL coronal plane (*A*: bregma −2.3 mm; *B*: bregma −2.7 mm). *Insets* (*top right*) of *A* and *B* depict the position of the plane related to the whole rat brain. *Inset* (*bottom right*) of *B* depicts the rat right forepaw: lp, lateral pad; mp, medial pad; w, wrist; d, digit; p, pad. The depth readings are in reference to the highest point of the pial surface, which is about 0.4 mm below bregma.

middle (mVPL), and caudal (cVPL). The rVPL carries mostly proprioceptive information and has large cutaneous receptive fields on the distal limb such as the entire forepaw or hindpaw. The mVPL is an area where the cutaneous RFs are focal and there is limited proprioceptive information. The cVPL appears to be an area of large receptive fields related to cutaneous stimulation and may preferentially convey cutaneous information that is specifically modulated by pain and visceral stimuli (Berkley et al. 1993; Gauriau and Bernard 2004; Guilbaud et al. 1993; Jahns 1975), although this may be speculative on our part because we did not specifically test such stimuli. These three subnuclei appear to run smoothly into one another and

into the nuclei that border them (McAllister and Wells 1981; Shiroyama et al. 1999).

There are several obvious trends in the rVPL. As with the rest of the VPL the forepaw is represented at the most medial aspect of the nucleus with the arm lateral to it followed by the hindpaw/hindlimb and finally the body (see figures). The representation of the forearm is expanded in the rVPL as is the hindlimb compared with the body. This trend can be seen throughout the VPL. We found it very difficult to find an obvious musculotopy past the aforementioned in the rVPL. With respect to individual muscles of the forearm we often found opposing muscle groups to be represented in the same
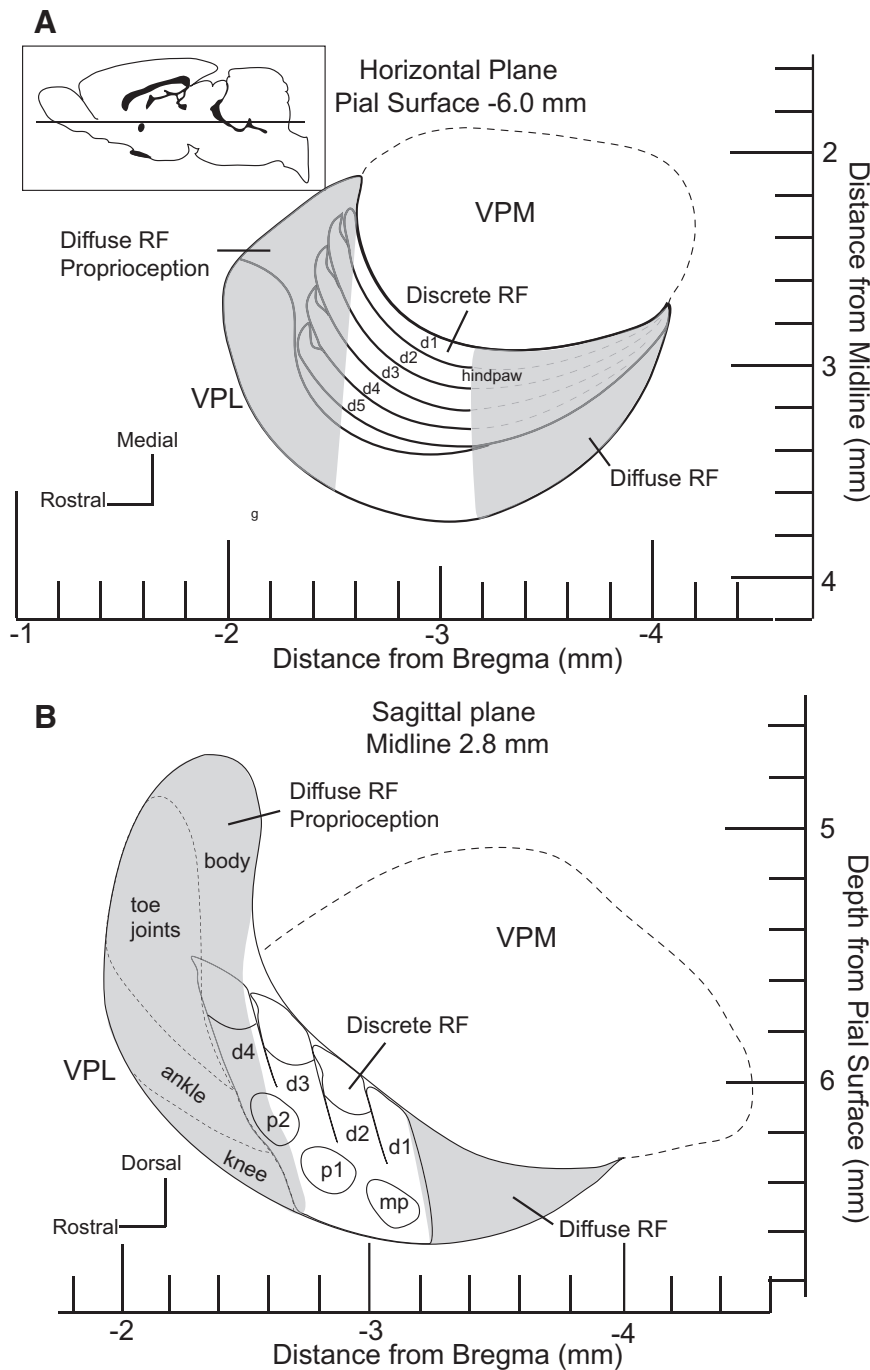
FIG. 7. Schematic drawing of somatotopy in the VPL horizontal plane (*A*, bregma −6.4 mm) and sagittal plane (*B*, midline 2.8 mm). *Insets* (*top left*) of *A* depict the position of the plane related to the whole rat brain: lp, lateral pad; mp, medial pad; w, wrist. Shaded areas in *A* and *B* depict the area where diffuse RFs were found. The depth readings are in reference to the highest point of the pial surface, which is about 0.4 mm below bregma.

recording site, but this was not always the case. In general, the overall trends seen in the mVPL for the fore- and hindpaws can be seen in the rVPL. However, the receptive fields are much broader with an average size on the fore- and hindpaw larger than a digit segment and often including much of or the entire paw. In one experiment we completely detached every muscle, starting from the wrist, working our way up the arm to the shoulder. With the electrode in a position −2.5 mm bregma, 2.5 lateral from the midline, and at a depth of 5.5 mm from the cortex surface we observed activity that was both fast adapting and nonadapting to shoulder movement. The nonadapting tonic activity was stopped only when both the pectoralis and biceps were removed. However, the fast adapting activity remained

even after all the muscles had been removed; thus it was due to joint receptors. This mixing of both joint and muscle receptors makes it nearly impossible to be certain of the exact RF; thus further experimentation is needed to determine whether there is a standard musculotopy in the rat rVPL because there is somatotopy. In addition, although we did not explicitly test well-isolated single units for responses to both cutaneous and proprioceptive stimulation, the multiunit responses would indicate that there is some overlap, and results from the cat corroborate this, although further study is warranted (Andersson et al. 1966).

There is evidence that the spinal cord circuitry has already processed the incoming proprioceptive information and trans-
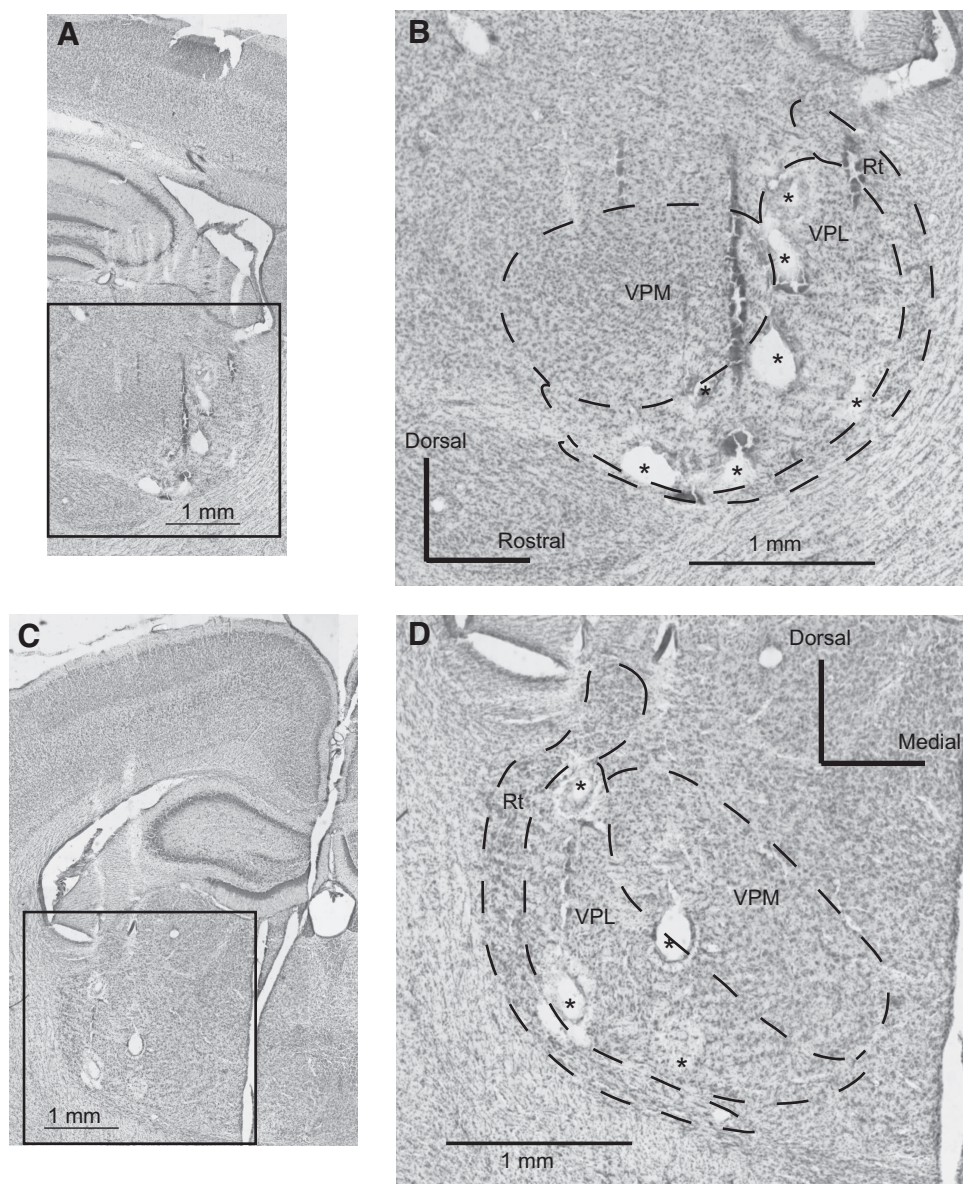
FIG. 8. Histological verification of mapping experiments. *A* and *B*: a sagittal section from a left hemisphere at about 2.8 mm from midline. *C* and *D*: a coronal section from a left hemisphere at about 3.0 mm posterior to bregma. *B* and *D* are magnified views of the marked area in *A* and *C*, respectively. The boundaries of reticular thalamic nucleus (Rt), ventral posterolateral thalamic nucleus (VPL), and ventral posteromedial thalamic nucleus (VPM) are superimposed in *B* and *D*. Note the visible electrode tracks and electrolytic lesions (marked with asterisks).

formed it into a higher level code (Bosco and Poppele 2000; Bosco et al. 2000; Poppele et al. 2002) and this may lead to a nonobvious musculotopy in the rVPL. There is also evidence that proprioceptive information coding step- cycle–like information runs in the spinothalamic tract of rats, which terminates partially in the VPL (Menetrey et al. 1984). Furthermore, there is similar evidence of step cycle or endpoint information of the forepaw seen in cuneate nucleus activity (Garifoli et al. 2002), which projects to the VPL. In addition, there are projections from the vestibular nuclei to the transition zone between the VL and the VPL, which most likely corresponds at least in part to our rVPL (Aumann et al. 1996; Shiroyama et al. 1999). With this in mind it is not surprising that we have found proprioceptive information expressed in the VPL.

Comparison with previous work

One of the first papers dedicated to determining the electrophysiological properties of the rat VP was that of Emmers (1965), which describes the somatotopic organization of both the VPM and the VPL. In a set of figures from this paper Emmers describes the somatotopy of the VP with the rostralmost area responding to whiskers medial to the forelimb with the body and hindlimb represented laterally in good agreement with our results, although at the rostral-most extent of the VP we did not find responses to whiskers. As one moved more caudally he found an area that he called the S2 portion of VP, where the receptive fields are less focal and more likely to be bilateral. His S1 portion of the VP is larger and rostral to the caudal S2 VPL. We would agree that in general the rostral half of the thalamus has more focal receptive fields than the caudal half, but that one can further divide the thalamus realizing that the receptive fields are most focal between −2.5 and −3.2 mm from bregma. We did not notice the prominence of bilateral information being carried by the VP thalamus in the areas that we studied extensively (−2 to −3.3 mm from bregma); admittedly this was not a goal of ours.

Tomasulo and Emmers (1970) followed up this earlier work with a study describing the effects that lesions to the spinal

cord had on defined response properties of VP cells. The authors concluded that the input to the "S1,", or rostral portion of the VP received inputs from the dorsal funiculus, whereas input to the "S2", or caudal VP came from the ventral quadrant as well as the dorsal portion of the lateral funiculus.

A second paper came out in 1965 describing the electrophysiological responses in the VP thalamus (Davidson 1965) with an interpretation different from that of Emmers. Davidson suggested that the bilateral responses seen in the caudal thalamus were in the posterior nuclear group, not the VP, and that relatively few bilateral responses could be seen in the VP. Both researchers were in agreement that the forelimb representation is medial to the hindlimb and the latter are represented in a thin strip with a smaller volume than that representing the forelimb and the whiskers.

Angel and Clarke (1975) described results from a large number of experiments, 304 animals yielding 505 single units that were included in their study. The results from this work are in general agreement with the aforementioned work. They described a small proprioceptive representation located in the ventral floor of the VP. We noticed a few proprioceptive units in this region as well, but clearly most of the proprioceptive activity courses through the rVPL.

There are some clear differences between our work and that of Angel and Clarke, which can be explained to some extent by the fact that they used a preparation such that the rat's head was on a declined angle with the nose pointing downward (the top of the incisor bar was 23° below the horizontal plane through the ear bars, whereas in Paxinos and Watson's preparation, the angle is about 5°). An important difference is that they did not appear to map out the rostral extent of the VP, where according to McAllister and Wells (1981), the size of the VP neurons is smaller and therefore may have been less probable to record from using the sharp glass electrodes with tips of 2–5 μm in diameter used by the former authors. In addition, according to Angel and Clarke the digits and the pads are at different coronal planes (see their Fig. 5), which is in complete disagreement with our findings. We found that many VPL units were spontaneously active in agreement with previous work (Cropper and Eisenman 1986; Davidson 1965). Angel and Clarke suggested that most VPL cells were completely silent until their receptive field was stimulated. This discrepancy between their work and ours cannot be explained by the different anesthetics used where they used urethane and we used pentobarbital in most of our studies and tested urethane as well in five experiments, with results indistinguishable from our pentobarbital experiments. Cropper and Eisenman used urethane for their experiments and found the VP units to be spontaneously active as well.

Anesthetics and VPL boundaries

In this study we used two different anesthetics: pentobarbital and urethane. We did not notice any obvious differences between the two as far as the somatotopy found in the VPL. Obviously we could not conduct our skin-off preparation in the unanesthetized rat, and conducting careful cutaneous mapping on an awake rat is rather difficult; however, perhaps in the future one could use a chronic recording implant while conducting mapping experiments using a paralyzing agent to deter-

mine whether the somatotopy remains as we have described here in the anesthetized state.

The mapping that we conducted was guided by our electrophysiological identification while being aided by the stereotaxic atlas of Paxinos and Watson (1998). As mentioned, we did conduct a set of five experiments after we had constructed our maps seen in Figs. 6 and 7 and made electrolytic lesions within the different regions of the thalamus (see Fig. 8). We cannot definitively state that at the rostral or caudal border we were in the "VPL" and not perhaps the VL or Po. It has been known for some time that there is a transition zone "between" the rostral VPL and the VL (McAllister and Wells 1981), and as referenced in Shiroyama et al. (1999). Irrespective of whether this transition zone belongs to the VPL or the VL may be up for debate. What is important is that we have for the first time described a large proprioceptive representation in the rat thalamus, which resides between approximately −2.0 to −2.5 mm from bregma. This area, and individual neurons within it, also respond to cutaneous stimulation with large receptive fields as we have described. Likewise, we cannot say that we did not map out portions of the posterior oral (Po) or a transition zone between the caudal VPL and the Po. According to McAllister and Wells there are transition zones between the VPL and the Po and VL and that these transition zones have responses representative of both nuclei. Thus further histological analysis is necessary to fully describe if our proprioceptive region is a transition zone, or in the VPL as it would appear using the rat atlas (Paxinos and Watson 1998).

Projections to and from the rat VPL

The literature corroborates our separation of the VPL into three zones. McAllister and Wells describe two transition zones between the VPL and the two nuclei that border its rostral and caudal extent, the VL and Po, respectively. According to these and other researchers (Gauriau and Bernard 2004; Lund and Webster 1967a,b) the spinal cord projects to the caudal and rostral portions of the VPL, but not as much to the middle third of the nucleus, which appears to be a zone showered by projections from the dorsal column nuclei (DCN). The DCN also sends projections throughout the VPL (McAllister and Wells 1981). This middle zone corresponds to our mVPL that is characterized by focal cutaneous receptive fields.

It has long been known that the VPL is a sensory nucleus that carries information from the spinal cord and dorsal column nuclei to the somatosensory cortex (Lund and Webster 1967a,b; Strick 1976). Both the DCN and the spinal cord project to the VPL carrying information on both pain and touch (Angel and Clarke 1975; Cropper and Eisenman 1986; Davidson 1965; Emmers 1965; Guilbaud et al. 1980) as well as proprioception (Angel and Clarke 1975; Low et al. 1986). There have been many studies concerned with the projections from both the DCN (Lund and Webster 1967a,b; Mantle-St John and Tracey 1987) and the various pathways of the spinal cord, most notably the spinothalamic tract to the thalamus. Lund and Webster (1967) stated that the projection from the spinothalamic tract (STT) is in general less dense to the VP thalamus than is the projection from the DCN, and that this (STT) projection is concentrated on the rostral one third of the VP with projections from the rostral few segments of the

cervical cord having an additional projection to the caudal VP; later results by McAllister (McAllister and Wells 1981) appear to agree with this. This latter projection from the rostral spinal cord to the caudal VP could be from the lateral cervical nucleus (Kajander and Giesler 1987). Some researchers suggested that representations of the same body parts project from the STT and the DCN to the same area in the VPL (Gauriau and Bernard 2004; Ma et al. 1986). These two systems synapse on different parts of VP neurons, with DCN projections synapsing on the somata and STT axons on the more distal dendrites (Ma et al. 1987; McAllister and Wells 1981).

The projections to the VPL that carry proprioceptive information appear to be segregated and send projections to the cerebellum as well. Mantle-St. John et al. (1987) described projections from the various brain stem nuclei to the VPL and cerebellum. These researchers found projections from the rostral cuneate (rCuneate) and lateral (external) Cuneate nucleus (Fukushima and Kerr 1979); both project to the cerebellum as well as the VPL, with neurons located in the ventromedial–caudal portion of the rCuneate projecting preferentially to the VPL and those in the rostral portion of the rCuneate projecting to the cerebellum. In the external Cuneate nucleus cells in the caudal portion project to the VPL, whereas those in the rostral portion project to the cerebellum. Nucleus X was found to project to both the cerebellum, as it does in the cat (Kotchabhakdi and Walberg 1978), and the VP thalamus with a larger projection to the cerebellum (Mantle-St John and Tracey 1987). Nucleus Z has been shown to project proprioceptive information to the VP thalamus in the cat (Mantle-St John and Tracey 1987). This nucleus has been shown to receive the same types of input in the rat (Low et al. 1986) and may also project to the VPL. There are also projections from the locus coeruleus, the solitary nucleus, and the lateral cervical nucleus (Fukushima and Kerr 1979). With the wide degree of projections into the VPL it is not surprising that it may have functional subnuclei that deal with different modalities of information such as pain, cutaneous sensation, and proprioceptive information.

Comparison of the rat VPL with primates

There is a good deal of evidence indicating that the VPL of primates has three architectonically distinct subnuclei with properties very similar to those we are proposing for the rat VPL. The rat is capable of using its "forepaws," which are more like hands, to grasp and retrieve food items (Whishaw and Tomie 1989), make reaching movements while holding onto a robotic manipulandum and compensating for force fields (Francis and Chapin 2004, 2006), as well as carry out texture discrimination reaching and grasping tasks (Ballermann et al. 2001). These are all tasks often associated with primates. If the structure of the VP nucleus is important in allowing these abilities to have developed evolutionarily, it may not be surprising that the rat's VP is similar to that of primates, although perhaps the rat VPL has not developed into the three architectonically distinct subnuclei seen in primates.

We have termed our three subnuclei the rVPL, mVPL, and the cVPL for rostral, middle, and caudal, respectively. In the primate literature the rVPL may correspond to the VPS (superior VP), which receives proprioceptive inputs from the brain stem and projects preferentially to areas 3a and 2 (Kaas et al.

1984). According to Huffman and Krubitzer (2001) the VPS corresponds with the "shell" region of the VPLc that is the caudal VPL that was described by Friedman and Jones (1981). In general, it seems that proprioceptive information in mammals flows rostrodorsal to the core cutaneous VPL (Kaas 2007; Wiener et al. 1987), whereas it lies rostral to the mVPL in the rat as seen in Figs. 2 and 7; it is in general also at a more dorsal level than is the mVPL.

The core cutaneous VPL (corresponding to our mVPL) receives cutaneous information from SA and RA receptors via the dorsal column nuclei and projects preferentially to areas 3b and 1 in monkeys (Kaas et al. 1984; Nelson and Kaas 1981) and, in general, to the primary somatosensory cortex in mammals. The general somatotopy in the mammalian VP is with the face most medial (VPM) followed by the forelimb and hindlimb as one moves laterally. It should be noted that the somatotopy in the rat VPL differs from primates in the fact that the fore- and hindpaw representations are inverted such that the tips of the digits are dorsal and the palmar pads are ventral, information that has been alluded to previously (Alloway et al. 2003; Angel and Clarke 1975). This inverted pattern is also seen in the flying fox (Manger et al. 2001).

The ventral posterior inferior nucleus (VPI) of primates receives information from the spinothalamic system and projects preferentially to the second somatosensory area (Friedman and Murray 1986; Stevens et al. 1993) and to a lesser extent S1 (Shi et al. 1993; Stevens et al. 1993). It has been reported that the vestibular nuclei project to VPI in the monkey (Deecke et al. 1974, 1977) and that the caudal VP complex in the cat projects to the parietal vestibular cortex (Blum et al. 1979). In the rat the caudal VP receives projections from the vestibular nuclei as well (Shiroyama et al. 1999). In addition, both the macaque VPI (Craig 2006) and the rat cVPL (Gauriau and Bernard 2004) receive projections from lamina 1 of the spinal cord, lending credence to our comparison of the rat cVPL with the VPI. Lamina 1 neurons of the macaque send a denser projection to the posterior ventromedial nucleus (VMpo) than to the VPI (Craig and Zhang 2006). In the rat, lamina 1 projections are strongest to a restricted portion of the cVPL; thus the cVPL in the rat may further differentiate into the VPI and the VMpo in the macaque.

In conclusion, we have presented evidence for a proprioceptive thalamic nucleus in the rat that lies in the rostral VPL (rVPL). We propose that this nucleus serves the purpose of the primate VPS in the rat and may be its evolutionary predecessor. The core cutaneous nucleus of the rat lies in the middle of the VPL (mVPL) and is the rat equivalent of the primate VPL, where the somatosensory receptive fields are focal. Caudal to the mVPL is a region where the receptive fields are broad and this region receives dense restricted projections from lamina 1 and may be the evolutionary predecessor of the VPI and the VMpo. Thus it is possible that during evolution this rostrocaudal orientation of the rat VPL was rotated such that the rVPL moved dorsal and the cVPL inferior, or ventral. In agreement with this rotation hypothesis, the VPL representation of the fore- and hindpaw of the rat is rotated with respect to the monkey VPL. Further histological analysis is necessary to determine whether these putative nuclei (rVPL, mVPL, and cVPL) are in fact separable and distinct.

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