



Posterior parietal cortex contains a command apparatus for hand movements

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Edited by Mortimer Mishkin, National Institute for Mental Health, Bethesda, MD, and approved February 7, 2017 (received for review May 20, 2016)

Mountcastle and colleagues proposed that the posterior parietal cortex contains a “command apparatus” for the operation of the hand in immediate extrapersonal space [Mountcastle et al. (1975) *J Neurophysiol* 38(4):871–908]. Here we provide three lines of converging evidence that a lateral region within area 5 has corticospinal neurons that are directly linked to the control of hand movements. First, electrical stimulation in a lateral region of area 5 evokes finger and wrist movements. Second, corticospinal neurons in the same region of area 5 terminate at spinal locations that contain last-order interneurons that innervate hand motoneurons. Third, this lateral region of area 5 contains many neurons that make disynaptic connections with hand motoneurons. The disynaptic input to motoneurons from this portion of area 5 is as direct and prominent as that from any of the premotor areas in the frontal lobe. Thus, our results establish that a region within area 5 contains a motor area with corticospinal neurons that could function as a command apparatus for operation of the hand.

motor control | motor systems | movement control | cerebral cortex

In a landmark paper, Mountcastle and his colleagues proposed that the posterior parietal cortex contains “a command apparatus for operation of the limbs, hands and eyes within immediate extrapersonal space” (1, p. 871). This hypothesis was based, in part, on the observation that some neurons in areas 5 and 7 were activated not by sensory stimuli but by the animal reaching for or manipulating a desired object. These “arm-projection” and “hand-manipulation” neurons were not active during other movements in which the same muscles were used. Instead, their activity was “conditional in nature” and dependent on the animal’s intention to explore the immediate surrounding space manually.

The development of the command hypothesis led Mountcastle and colleagues to reinterpret some of the consequences of parietal lobe damage: “We propose that several of the abnormalities of function that occur in humans and in monkeys after lesions of the parietal lobe can be understood as deficits of volition, of the will to explore with hand and eye the contralateral half-field of space ...” (1, p. 905) and “We infer that these defects reflect the loss of a particular source of commands for movement” (1, p. 901).

The command hypothesis represented a fundamental paradigm shift in concepts about the function of the posterior parietal cortex. The prevailing view at the time was that the cortical areas within the posterior parietal cortex were part of the “association cortex.” These cortical regions were thought to construct higher-order sensory representations based on input from primary and secondary sensory areas. In addition, they were thought to play a role in the integration of information from multiple sensory modalities. The results of this integration then could be used by other cortical areas and subcortical motor centers to guide movement. The command hypothesis was novel in viewing the posterior parietal cortex as containing a mechanism to construct and issue motor command signals for movements made to objects of interest in the immediate extrapersonal space. The command hypothesis was supported by the demonstration of inputs from the posterior parietal cortex to motor areas in the frontal lobe that could mediate the parietal commands to the spinal cord for execution (2–5).

Here we show that a lateral region within area 5 has a disynaptic projection to hand motoneurons in the spinal cord. We provide evidence that this disynaptic connection is mediated by corticospinal connections with last-order interneurons that project to distal hand motoneurons. This connection provides the posterior parietal cortex with the potential to control motoneuron activity directly at the spinal level.

Results

Intracortical Stimulation in Lateral Area 5. In two rhesus monkeys, we used intracortical stimulation (0.2-ms cathodal pulses, 333 Hz, 100- to 200-ms train duration, 10–300 μ A) to map the motor representation in a lateral region of area 5. We explored cortex in the anterior bank of the intraparietal sulcus (PEip) and on the adjacent cortical surface (PE) along a 5-mm region beginning at the lateral edge of the intraparietal sulcus (IPS) (Fig. 1*A* and *B*). We mapped this region because prior studies have shown it projects to the spinal cord (6–9) and because cortical neurons with disynaptic input to hand motoneurons are located there (see below).

Stimulation in this lateral region of area 5 reliably evoked movements of the contralateral hand in 25 of 35 sites tested (Fig. 1*B*). The threshold for evoking movement was as low as 50 μ A (in two sites) but generally was higher (166 ± 55 μ A, mean \pm SD). In most instances, stimulation evoked movements of the thumb and finger in isolation (22 sites). Combined thumb and finger movements were evoked at two sites, and combined wrist and finger movements were evoked at one site. These results are consistent with the many prior studies that have been able to

Significance

The primate hand has evolved into a specialized sensorimotor device that can grasp, explore, and manipulate objects with extraordinary skill. The frontal lobe is generally thought to be the exclusive source of descending commands to the spinal cord to control hand movements. Here, we identify a region within the parietal lobe that could also contribute commands to control hand movements directly at spinal levels. Intracortical stimulation in a lateral region in area 5 of posterior parietal cortex reliably evokes hand movements. Corticospinal neurons in this region make disynaptic connections with hand motoneurons. These observations suggest that a region within lateral area 5 contains a unique command apparatus that could assist in generating dexterous finger movements required during haptic behavior.

Author contributions: J.-A.R., R.P.D., and P.L.S. designed research, performed research, analyzed data, and wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

Freely available online through the PNAS open access option.

See Commentary on page 4048.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1608132114/-DCSupplemental.

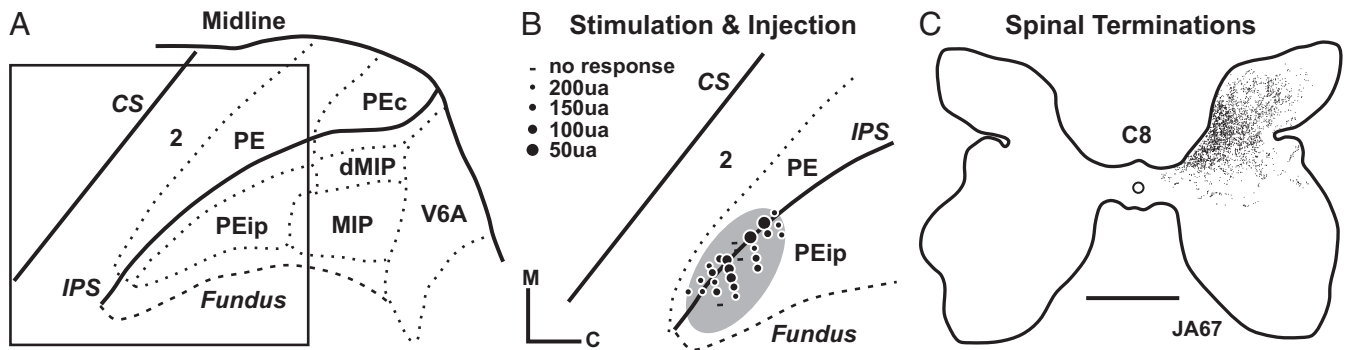


Fig. 1. Lateral area 5: intracortical stimulation effects and spinal terminations. (A) Subdivisions of area 5 (adapted from ref. 42, with permission from Oxford University Press). The box defines the region displayed in *B* and in Figs. 5 and 6. (B) Map of stimulation sites and CTb injection in area 5 in monkey JA67. The small filled circles mark the sites of stimulation and the threshold for a motor effect (see key). The shaded area indicates the extent of the CTb injection. (Vertical and horizontal scale bars: 2 mm.) (C) Anterograde labeling at C8 (fine stippling) from the CTb injection into lateral area 5 shown in *B*. (Scale bar: 1 mm.) C, caudal; CS, central sulcus; dMIP, medial intraparietal area dorsal part; IPS, intraparietal sulcus; M, medial; MIP, medial intraparietal area; PE, area PE; PEc, area PE caudal part; PEip, area PE in the intraparietal sulcus; V6A, area V6A.

evoke a range of limb, eye, or face movements by intracortical stimulation in regions of the posterior parietal cortex (5, 10–14). One of these prior studies demonstrated that finger and grasping movements could be evoked by stimulation in a lateral portion of area 2 on the cortical surface of macaques (5). Our results extend this observation by demonstrating a distal hand representation in a lateral region of area 5 within the IPS.

Spinal Termination of Efferents from Lateral Area 5. We placed multiple, small injections of cholera-toxin subunit B [CTb, 2% (vol/vol) in distilled water] into the hand representation defined by intracortical stimulation (shaded region in Fig. 1*B*). Then we used anterograde transport of the tracer to define the pattern of termination of efferents in cervical segments (C2–T2) of the spinal cord (Fig. 1*C* and Fig. S1*B*). We observed labeling exclusively on the side of the spinal cord that was contralateral to the cortical injection. We found CTb labeling throughout segments C2–T2 in portions of Rexed laminae II–VII (Fig. 1*C* and Fig. S1*B*). The labeling was densest at C8 medially in portions of laminae IV–VI. The pattern of spinal terminations that we observed is similar to findings reported for efferents from “area 2/5” (15) but is different from another study of terminations from “area 5” (16). The variation in these findings likely results from the involvement of different portions of areas 2 and 5 in the injection sites.

Last-Order Interneurons Innervating Hand Motoneurons. We injected single hand muscles of two rhesus monkeys with rabies virus (N2c strain) and used retrograde transneuronal transport of the virus to identify the last-order interneurons in the spinal cord with monosynaptic input to hand motoneurons. One of these animals received an injection of rabies virus into the abductor pollicis longus (APL), and the other received an injection into the extensor digitorum communis (EDC). The survival time in these animals was just long enough to allow virus transport to second-order neurons in the spinal cord (Fig. 2*A*, filled neurons designated “2 IN” in the diagram) but was not long enough to allow transport to other second-order neurons at more remote sites, such as the red nucleus and cerebral cortex (Fig. 2*A*, filled neurons designated “2 RM” and “2 CM,” respectively, in the diagram).

The distribution of second-order neurons in the spinal cord was comparable in these two animals. In both, we found labeled interneurons bilaterally mainly in spinal segments C4–T3 (Fig. 3 and Fig. S1*A*). However, the great majority (90–95%) of the labeled interneurons were located in spinal gray matter ipsilateral to the injected muscle. We found labeled interneurons distributed throughout Rexed laminae IV–VIII (Fig. 3*A* and Fig. S1*A*). Dense clusters of

labeled interneurons were present in both the dorsal horn, especially medially, and in the intermediate zone of the spinal cord.

Along the rostro-caudal axis, labeled interneurons displayed a unimodal distribution that peaked in C8 but extended as far rostrally as mid C2 and as far caudally as mid T4 (Fig. 3*B*, small filled circles). Even so, 91–96% of all labeled interneurons were found in segments C5–T2. The peak in the distribution of interneurons is slightly rostral to the peak in the distribution of APL and EDC motoneurons in lamina IX (Fig. 3*B*, small filled squares; also see ref. 17).

We next compared the distribution of corticospinal terminations from the injection sites in lateral area 5 with the distribution

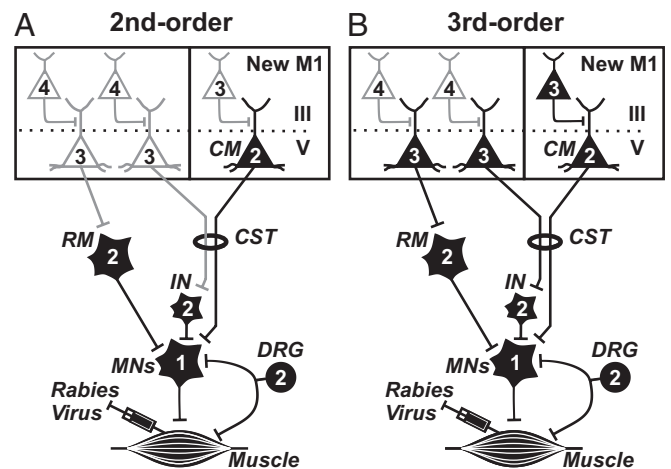


Fig. 2. Circuits mediating retrograde transneuronal transport of rabies virus from single muscles. (A) Labeling of second-order neurons. After an injection of rabies virus into a single muscle, virus is transported in the retrograde direction to infect first-order neurons (1) that innervate the muscle (motoneurons, MNs). Then, virus moves transsynaptically in the retrograde direction to infect second-order neurons (2) that make monosynaptic connections with the infected motoneurons. These neurons include spinal interneurons (IN), rubromotoneuronal (RM) cells, dorsal root ganglion (DRG) cells that innervate muscle spindle afferents, and corticomotoneuronal cells (CM) in New M1 layer V (18, 19). (B) Labeling of third-order neurons. At longer survival times, rabies virus undergoes another stage of retrograde, transneuronal transport to infect third-order neurons (3) that make monosynaptic connections with the infected second-order neurons. Labeled third-order neurons include corticospinal neurons in layer V of cortical areas such as the Old M1 (ref. 19), corticorubral neurons in layer V of the cerebral cortex, and neurons in layer III of New M1. CST, corticospinal tract.

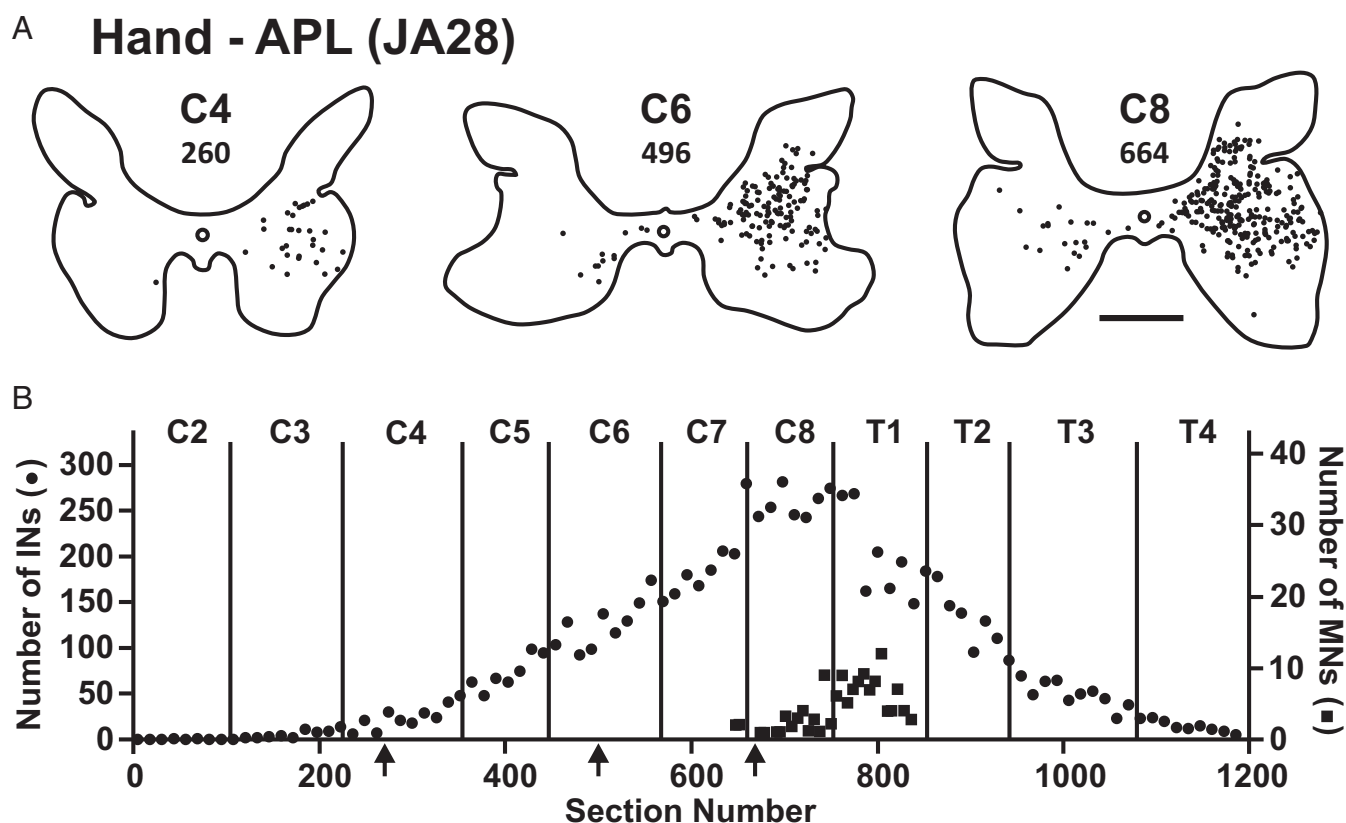


Fig. 3. Location of interneurons (INs) in the spinal cord that innervate APL. (A) Charts of the gray matter from selected coronal sections of the spinal cord at levels C4, C6, and rostral C8. The small filled circles indicate the location of the spinal interneurons that were labeled after retrograde transneuronal transport of rabies virus from the APL. (Scale bar: 1 mm.) (B) Distribution of interneurons along the rostro-caudal axis of the spinal cord. The filled circles indicate the location of the spinal interneurons that were labeled after retrograde transneuronal transport of rabies virus from the APL. The filled squares indicate the location of APL MNs (motoneurons) (data from ref. 17). Arrows along the abscissa in B indicate the levels of the sections shown in A.

of last-order spinal interneurons innervating APL and EDC motoneurons (Fig. 4 and Fig. S1). Although these experiments were performed in different animals, it is clear that the medial region of the dorsal horn where corticospinal terminations are the densest (Rexed laminae IV–VI) also contains last-order interneurons that innervate hand motoneurons (Fig. 4C). For example, the overlap between corticospinal terminations and last-order interneurons is clearly evident at C8. CTb terminations from the injection site into lateral area 5 were especially dense medially in the dorsal horn (Fig. 4B). The same region of the dorsal horn contains substantial numbers of second-order neurons infected through retrograde transneuronal transport of rabies virus from a virus injection into APL (Fig. 4A). In the next section we provide evidence that this overlap reflects synaptic input from corticospinal efferents in lateral area 5 to last-order interneurons innervating hand motoneurons.

Disynaptic Connection from Lateral Area 5 to Hand Motoneurons. In seven monkeys, we used transneuronal transport of rabies virus from single muscles to define regions of the cerebral cortex that contained neurons with disynaptic input to motoneurons. To do so, we adjusted the survival time to label third-order neurons in the cerebral cortex (designated “3” in Fig. 2B). We placed virus injections into single hand (EDC; $n = 2$; APL; $n = 1$), elbow (long head of biceps, BIC; $n = 2$), and shoulder (spinodeltoid, SPD; $n = 2$) muscles.

Cortical areas with third-order neurons included the portion of area 4 on the surface of the precentral gyrus (“Old M1”), the portion of area 4 in the anterior bank of the central sulcus (“New M1”), several premotor areas in the frontal lobe, and, notably, a

lateral region of area 5 (Figs. 5 and 6) (see also refs. 18 and 19). Third-order neurons in area 5 were found in lateral parts of areas PE and PEip on the convexity of the post central gyrus and in the anterior bank of the IPS (Figs. 5 and 6). Small numbers of labeled neurons also were present in adjacent portions of somatosensory area 2. As expected from our prior studies, labeled neurons in the New M1 were located in supra- and infra-granular layers as well as in layer V (see figure 5 in ref. 19). In contrast, the labeled neurons in all other cortical areas, including the lateral portion of area 5, were confined to layer V.

The absolute number of third-order neurons labeled in different cortical areas varied from animal to animal (Table S1). In general, we found more third-order neurons labeled in the Old M1 and in the dorsal premotor area (PMd) after virus transport from proximal muscles than after transport from distal muscles (Table S1). In contrast, we found many more third-order neurons labeled in the lateral portion of area 5 after virus transport from distal muscles than after transport from proximal muscles (Figs. 5 and 6).

For comparisons across animals (Table S1), we grouped animals according to the muscle injected: proximal or distal (Fig. 7). Then we normalized the data from animals relative to the number of neurons labeled in the Old M1. This analysis revealed that virus transport from proximal and distal muscles labeled comparable percentages of third-order neurons in the PMd. On the other hand, the percentage of labeled neurons in the lateral region of area 5 after virus injections into distal muscles was 20 times greater than the percentage labeled after transport from proximal muscles (Fig. 7). Thus our results indicate that a lateral region of area 5 has representations of the proximal and the

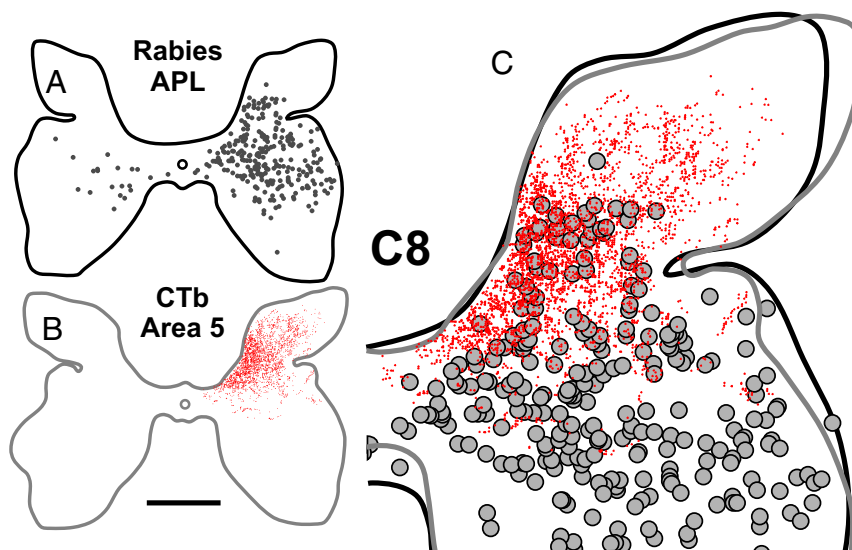


Fig. 4. Spinal overlap of terminations from area 5 and interneurons that innervate APL motoneurons. (A) Location of interneurons (filled circles) that innervate APL motoneurons (see C8 in Fig. 3A). (B) Location of spinal terminations (red dots) originating from neurons in lateral area 5 (see Fig. 1C). (C) A superimposition of an enlarged portion of the sections in A and B illustrates the extensive overlap of these two elements, especially in a dorsomedial region of the spinal cord. (Scale bar: 1 mm for A and B, 0.3 mm for C.)

distal forelimb, but the distal representation is clearly larger both in terms of its size (Figs. 5 and 6) and the number of output neurons (Figs. 5–7). In addition, although the relative number of third-order neurons in the hand representation in lateral area 5 is less than half that in Old M1, the relative number in the hand representation of lateral area 5 is more than 1.5 times that in the PMd. This result raises the possibility that a lateral region of area 5 has a more substantial influence over the generation of hand movements (at the spinal level) than the PMd.

Discussion

Overall, we provide three lines of converging evidence that a lateral region within area 5 has corticospinal neurons that are directly linked to the control of hand movements. First, electrical stimulation in a lateral region of area 5 evokes finger and wrist movements. Second, corticospinal neurons in the same region of area 5 terminate at spinal locations that contain last-order interneurons that innervate hand motoneurons. Third, the lateral region of area 5 contains many neurons that make disynaptic connections with hand motoneurons. The disynaptic input to motoneurons from area 5 is as direct and prominent as that from any of the premotor areas in the frontal lobe. Thus, our results establish that a lateral region of area 5 contains a motor area with corticospinal neurons that could function as a command apparatus for operation of the hand.

In support of the concept that a portion of posterior parietal cortex contains a motor area, Gardner and colleagues have found neurons in the lateral region of area 5 that discharge during the manipulation of objects (20–22). In fact, the firing rates of many neurons at this site increase before the hand makes contact with an object, peak at object contact, and decline when grasp of an object is secure (21, 23). These observations suggest that neurons in this lateral region of area 5 contribute to the initiation of hand movements required for grasping and manipulating objects.

Lateral area 5 is not the only region in the parietal cortex that is involved in motor control of the hand and arm. Other portions of areas 5 and 7 in the superior and inferior parietal lobules contain regions that are involved in different aspects of reaching and grasping (for references and reviews see 24, 25, 26, and 27). In addition, Gharbawie et al. (5) found that hand movements can be evoked from a region of area 2 that is just rostral to the motor

area we identified. However, the motor area in lateral area 5 is unique among these parietal modules in having relatively direct access to motor output via corticospinal neurons that make disynaptic connections with hand motoneurons.

It is noteworthy that corticospinal neurons in lateral area 5 gain access to motoneurons in a manner comparable to other motor areas in the frontal lobe. Specifically, the region of medial lamina V–VI that receives corticospinal input from lateral area 5 also receives corticospinal input from M1, the supplementary motor area, and the caudal cingulate motor areas on the dorsal and ventral banks of the cingulate sulcus (28). Thus, this spinal region may be a site where multiple descending systems converge on a set of last-order interneurons that influence the control of hand movements.

In the cat, the same region of medial lamina V–VI contains interneurons that receive input from cutaneous afferents (29).

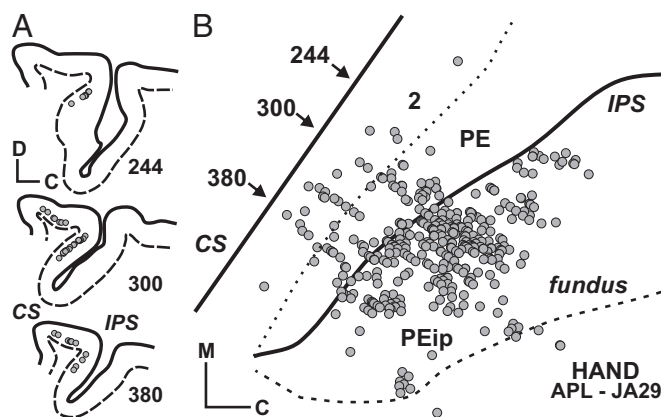


Fig. 5. Location of corticospinal neurons in area 5 that make disynaptic connections with APL motoneurons. (A) Selected parasagittal sections through the IPS show third-order neurons (small circles) labeled by retrograde transneuronal transport of virus from an injection into the APL. (B) Flattened reconstruction of lateral area 5 showing the distribution of third-order neurons (small circles) that make disynaptic connections with APL motoneurons. The arrows indicate the levels of the sections in A. (Vertical and horizontal scale bars: 2 mm.) C, caudal; CS, central sulcus; D, dorsal; IPS, intraparietal sulcus.

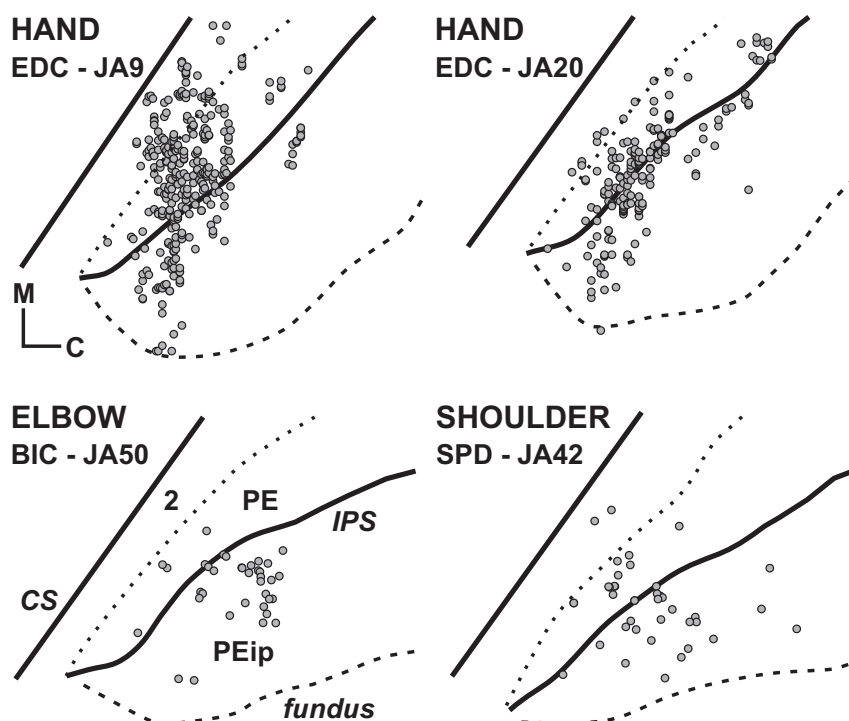


Fig. 6. Distribution of corticospinal neurons in lateral area 5 that make disynaptic connections with the motoneurons that innervate hand (EDC), elbow (BIC), or shoulder (SPD) muscles. Conventions are as in Fig. 5B. (Scale bars: 2 mm.)

Many of these interneurons receive excitatory input from corticospinal (and rubrospinal) efferents and are last-order interneurons that excite or inhibit motoneurons that innervate distal forelimb muscles (30). It is tempting to speculate that corticospinal efferents from lateral area 5 of the monkey are activating this system of interneurons. If so, the input from lateral area 5 could function to regulate the flow of somatosensory information to hand motoneurons and assist in the command of finger movements involved in active touch during haptic behavior.

This proposal fits with the consequences of posterior parietal lesions in humans at sites potentially homologous to the motor area in lateral area 5. The lesions in humans typically induce tactile apraxia, which is characterized by “severe abnormalities of exploratory finger movements, despite normal frequencies of repetitive finger movements and almost normal force production” (31). The deficit in tactile apraxia appears to represent an isolated disturbance of the fine dexterous hand movements that are required to interact with an object. A similar, although less dramatic, deficit has been observed in the monkey following lesions to lateral area 5 (32). Tactile apraxia in humans is generally accompanied by an impairment of tactile gnosis (astereognosis). Thus, corticospinal signals originating from lateral area 5 could be part of a command system for active touch that requires the tight interplay between tactile perception and fine finger movement.

The existence of a motor area in lateral area 5 is surprising given the classical view that the central sulcus represents the functional dividing line between motor and sensory cortex. According to this view, cortical areas anterior to the central sulcus are involved in the generation of movement and are the main source of descending motor commands to the spinal cord. In contrast, cortical areas posterior to the central sulcus are involved in processing sensory information and are the target of ascending signals about events occurring in the periphery (however, see ref. 33). Mountcastle’s command hypothesis clearly violated this functional subdivision because it proposed that the posterior

parietal cortex generates commands for movements in immediate extrapersonal space (1). Subsequent studies demonstrated the presence of dense projections from the posterior parietal cortex to motor areas in the frontal lobe that could mediate the parietal

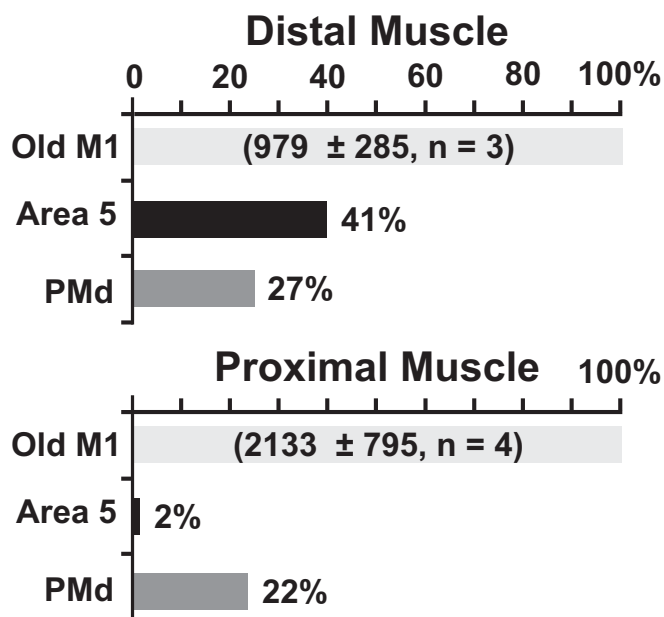


Fig. 7. Comparison of area 5 and the PMd: disynaptic connections with motoneurons. The numbers of labeled neurons in area 5 and the PMd were normalized to the number of labeled neurons in Old M1 (Table S1). Horizontal bars indicate the mean percent of labeled neurons relative to Old M1. The PMd was selected for comparison because it was the premotor area with the greatest number of disynaptic connections to forelimb motoneurons.

commands to the spinal cord for execution (2–5). Our findings are noteworthy because they show that a localized region within the posterior parietal cortex has a direct anatomical route to access motor output at the spinal level. In fact, the access to motor output from lateral area 5 is comparable to that from the premotor areas in the frontal lobe. These data clearly fit Mountcastle's view that the posterior parietal cortex has a command function. This view also is supported by the classic observations of Fleming and Crosby (34) that the motor responses evoked by electrical stimulation of the posterior parietal cortex persist even after removal of the motor cortex. Our results provide further support for the perspective that the central generation and control of movement depends on descending commands from multiple cortical motor areas, now including a portion of lateral area 5 (35). Indeed, Mountcastle and colleagues emphasized that the "concept of command centers explicitly assumes that there exist within the central nervous system many sources of commands to the motor apparatus" (1, p. 902).

Materials and Methods

This report is based on 11 adult rhesus monkeys (*Macaca mulatta*). In two animals (JA65: male, 13 y old, 10.4 kg, and JA67: female, 4.4 y old, 4.8 kg), we used intracortical stimulation to map a lateral region in area 5 before an

injection of a conventional anatomical tracer, CTb. In the remaining nine animals (five males and four females, 2.9–4.9 y old, 3.3–5.7 kg), we injected rabies virus into a single forelimb muscle.

All experimental procedures were conducted in accordance with National Institutes of Health guidelines and were approved by the relevant Institutional Animal Care and Use and Biosafety Committees. The procedures for handling rabies virus and animals infected with rabies have been described previously (36, 37) and are in accordance with or exceed the recommendations from the Department of Health and Human Services (Biosafety in Microbiological and Biomedical Procedures). Most of our procedures have been described fully in prior publications (for intracortical stimulation and tracer injections, see refs. 38–41; for injections of rabies virus into single muscles, see refs. 18 and 19) and are summarized in *SI Materials and Methods*. The data that support the findings of this study are available from the corresponding author upon request.

ACKNOWLEDGMENTS. We thank Dr. M. Schnell (Thomas Jefferson University) for supplying the N2c strain of rabies; Dr. A. Wandeler (Animal Disease Research Institute) for supplying the antibody to the rabies virus; M. Page and M. Semcheski for the development of computer programs; and Ms. M. Watach, M. Carrier, M. O'Malley, and D. Sipula for technical assistance. This work was supported in part by funds from NIH Grants R01 NS24328 (to P.L.S.) and P40 OD010996 (to P.L.S.). This project also was funded in part by a grant from the Pennsylvania Department of Health, which specifically disclaims responsibility for any analyses, interpretations, or conclusions.

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