Communications

Testing Peripheral Somatosensory Neuroprostheses by Recording from Raccoon Cortex

Charles J. Robinson, Robert D. Wurster, and James S. Walter

***Abstract*—A topologically organized representation of the body surface exists within the mammalian somatosensory cortical areas such that stimulation of a part of the body surface will produce a response in a localized region of the contralateral somatosensory cortex. Because of this topography, we propose that the selectivity of a peripheral somatosensory neuroprosthetic electrode array can be tested by noting whether the locus of maximum activation in the cortex moves in a consistent manner when differing portions of the array are stimulated. We further propose that the raccoon might well be the ideal animal in which to test this hypothesis, since the raccoon has a rather unique cortical somatosensory area where each digit is represented in individual subgyri around the tri-radiate sulcus. To demonstrate the feasibility of this concept, a pilot study was carried out in one raccoon under barbiturate anesthesia. The median nerve was stimulated via selective quadrants of a nerve cuff array of four tripolar electrodes implanted around the nerve. Cuff stimulation produced short-latency evoked surface potentials in the digit areas of the raccoon first somatosensory cortex. Response selectivity could be demonstrated, as could a separation between thresholds for producing movement or producing cortical evoked potentials. The sensory and motor responses elicited were consistent with the orientation of the median nerve within the cuff as determined by a postmortem identification of the muscle innervation pattern of the nerve.**

I. Introduction

Various neuroprosthetic devices, such as cuff electrodes, penetrating electrode arrays, or electrode "channels," can be used to activate selective portions of a peripheral nerve [1], [4], [12], [14], [19]. When these devices activate efferent axons, their effectiveness can readily be seen by visually observing the movement produced by the stimulation or through quantitative measurements using torque and angle sensors.

The same neuroprosthesis can be used to activate somatic afferents. However, quantifying the somatosensory response is not as straightforward. If a sensory neuroprosthesis were to be placed in a human, one could rely on a verbal response or use various psychophysical methods to determine the relationship between stimulus and a perceived tactile sensation. But before a device can be used in humans, its efficiency must be demonstrated in animals. A device could be tested in primates trained via psychophysical techniques to discriminate the intensity or location of a tactile stimulus, although such training is time- and labor-intensive. Certainly, many primates have been trained to grade the intensity of a tactile stimulus, although training them to make fine discriminations in the location of a stimulus is exceedingly difficult [15].

Humans, primates and other mammals all have localized regions of their cerebral cortex devoted to somatic sensation [10]. Within these somatosensory cortical areas, a topologically organized representation of the body surface exists, such that stimulation of different body surfaces or peripheral nerves will produce a response in a different part of the contralateral somatosensory cortex. One could thus test the selectivity of a peripheral somatosensory neuroprosthetic electrode array by noting whether the locus of maximum activation in the cortex moves in a consistent manner when various portions of the array are stimulated.

The proportional amount of cortex devoted to a particular body part in a given species correlates well with the type of tactile information important to the species. The proportional representation of the hand and finger surfaces is greatest in the human, primate, and raccoon, since all three species rely heavily on manual dexterity [10]. The cortical neuroanatomy of the raccoon is unique in that each digit is represented in individual subgyri around the tri-radiate sulcus (see Fig. 1, modified with permission from [18]). These gyri provide easily recognizable landmarks for electrode placement. Since appropriate ethical, regulatory and cost issues impede the use of human and primate species for routine preclinical testing, and since the raccoon is bred commercially and readily available for research purposes, we propose that the raccoon might well be the ideal animal in which to test whether a peripheral somatosensory neuroprosthesis devoted to the hand or fingers can activate an appropriate localized region in the hand and digit area of somatosensory cortex.

The precision of this cortical mapping in the raccoon prompted us to perform a pilot experiment. We investigated the selective centripedal effects of stimulating the median nerve with a nerve cuff electrode that has four sets of tripolar electrodes spaced at 90° intervals around the nerve [Fig. 2(a)]. We had previously studied the chronic effects of implantation of this cuff [17], and the selectivity of the cuff in producing movements of the raccoon forelimb, wrist and digits [1], [16].

We [16] and others [3], [11], [12], [14] have already demonstrated that selective stimulation with such a cuff can produce discrete and separable movements in the muscles innervated by a multifascicular nerve and that muscle force can be graded by increasing the stimulus intensity. We wondered whether a similar separation could be found within that part of the somatosensory cortex that is activated from the median nerve. If such a selective activation were to be found, it could have immediate clinical application in the restoration of the tactile sense to individuals with upper limb amputation. The signals from artificial tactile sensors could be used to control the magnitude and location of stimulation to the residual nerve trunk.

As a pilot study to demonstrate the feasibility of this concept, a cortical mapping experiment was carried out in one raccoon who had in place a nerve cuff electrode on its median nerve. This raccoon was one of four in which such a cuff had been acutely implanted to

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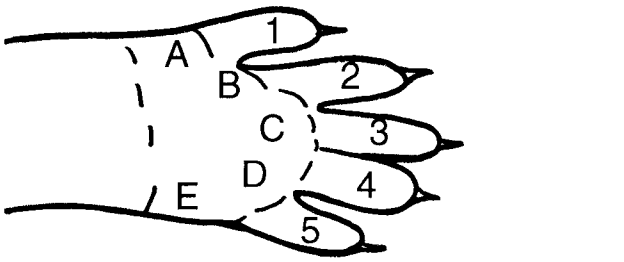
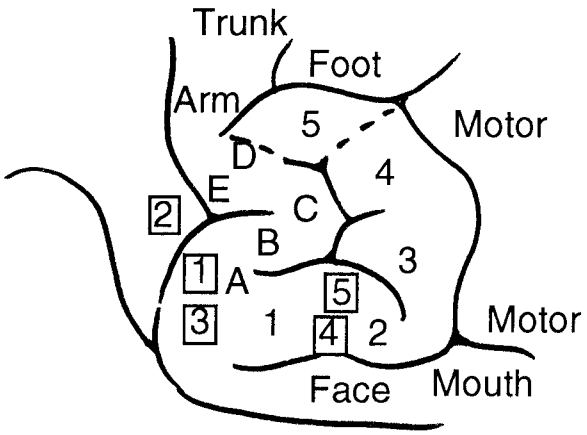


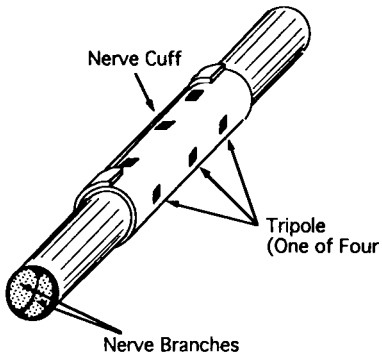
Bipolar Recordings in
Tri-radiate Sulcus of Racoon

(a)

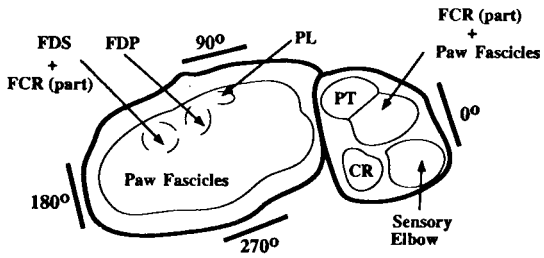


(b)

Fig. 1. Tri-radiate sulcal area of the raccoon right cortex (b), where individual gyri can often be identified with the somatosensory cortical representation of an individual contralateral digit. The letters and unboxed numbers on the gyri map to the location of the respective receptive fields on the left digits and palm (a). The boxed numbers represent the loci of surface recording sites described in this paper. (This figure is a modification of [18, Fig. 9], and is used with permission of Wiley–Liss, Inc, a subsidiary of John Wiley and Sons, Inc., who copyrighted the original figure from [18] in 1959.)



(a)



(b)

Fig. 2. (a) Twelve-element, tripolar nerve cuff electrode. (b) The orientation of the electrode on the two branches of the median nerve and the relative muscle innervation pattern of the nerve as determined by postmortem dissection. Fascicles to pronator teres (PT), flexor carpi radialis (FCR or CR), palmaris longus (PL), flexor digitorum superficialis (FDS), and flexor digitorum profundus (FDP) were identified.

study the ability of the cuff to produce selective movements of the digits, hand and wrist; and to study the forces produced in individual tendons by selective stimulation of the cuff. For clarity, an overview of the animal preparation used for the movement studies is presented in the next section.

II. Methods

A. Animal Preparation

The raccoon (Procyon Lotor) used for the movement studies and this cortical response study was bred for research (Hummal Creek Kennels, St. Louis, MO) and weighed approximately 4 kg. Ketamine hydrochloride (20 mg/kg) and xylazine (2 mg/kg) were used as initial induction agents. The raccoon was intubated, placed on a respirator and maintained on pentobarbital anesthesia (P.R.N. intraperitoneally). The deep and superficial branches [16] of the median nerve in the upper left forelimb were surgically exposed and identified electrophysiologically via bipolar nerve stimulation. A multi-electrode spiral cuff was then inserted that snugly encircled both branches.

The 12-electrode nerve cuff has been well described elsewhere [3], [11], [12], [14]. It consists of four longitudinal rows of three 1 mm platinum "dots," with each row located 90° apart [Fig. 2(a)]. The middle dot of each row serves as the stimulation cathode, while the two outer dots of each row are electrically connected and serve as the anode. A "steering current" could also be employed by additionally anodically stimulating the center electrode located 180° from the cathodic electrode [9]. The electrode dots were placed on an elastomer material that caused the assembly to curl into a spiral tube [6] that was then placed around the nerve. Each quadrant of the tripolar sets was individually stimulated, while taking note of any cortical evoked response or evoked movement. The 10 μs stimulus pulse was generated by a two channel Grass constant current stimulator (Grass Model S11 with SIU7 isolator), either as a single stimulus or with a repetition rate of 1/s (for cortical responses) or 20/s (for movement responses).

Videographic recordings were made of the discrete muscle movement produced by stimulation of each quadrant of the cuff, with stimulus current set to a) the threshold for movement, b) the lowest intensity that produced a maximal movement response, and c) one half this maximal current. The relevant results for conditions a) and c) are reproduced in Table I of this paper.

After the videographic recordings were completed, the forearm was dissected down through the middle of the palm and the tendons of the extrinsic muscles of the paw and wrist were isolated and attached

TABLE I
A COMPARISON OF PERIPHERAL MOVEMENTS AND SOMATOSENSORY CORTICAL POTENTIALS EVOKED BY STIMULATION OF ONE OF THE FOUR QUADRANTS OF THE CUFF ELECTRODE

STIMULATING ELECTRODE	0° (top)	90° (medial)	180° (bottom)	270° (lateral)
MOTOR RESPONSE (From Reference 17, Tables 1 and 2, Raccoon #3) 10 μsec pulses, 20 pps for 1 sec				
Movement @ Threshold	pronate, 0.2 ma	wrist, digits, 0.2	wrist, digits, 0.2	elbow, 0.3
Movement @ 1/2 max.	elbow,wrist, 0.7	wrist, elbow,0.6	wrist, digits, 0.5	elbow,wrist, 0.7
Muscles active @ thresh (as determined by force on tendon)	pronator teres	Palmaris longus Flex. digit. profundus Flex. digit. superficialis	Palmaris longus Flex. digit. profundus Flex. digit. superficialis	Flex. Carpi radialis
CORTICAL RESPONSE Evoked potential thresholds determined by stimulation with a single pulse. Tendons were cut, so concurrent movement could not be precisely mapped				
Recording Location #1	Sensory RF=lateral base of D1 + medial base of D2			
response @ current	small amplitude response @ 2ma	excellent response @1ma	excellent response @1ma	distinct, but small @1ma
Recording Location #2	Sensory RF= none (Recording site most posterior)			
Recording Location #3	sensory RF= web b/t D1/2, D2/3, D3/4, D4/5 (radial) - (Recording site far lateral of #1)			
EP, max resp threshold	<0.1 ma, <0.1 ma	0.4 ma, 1.5 ma	0.5 ma, 0.6 ma	<0.1 ma, <0.1 ma
Recording Location #4	sensory RF could not be found (recording anterior to #3) - Note that palm was dissected			
Threshold for EP	0.1 ma	0.5 ma	0.7 ma	0.2 ma
Recording Location #5	sensory RF= glab. skin, medial part of D2			
Threshold for EP	0.2 ma	0.5 ma	0.5 ma	0.1 ma

to force transducers (Grass). We determined the relative activation, recruitment profiles, and peak forces generated in pronator teres (PT), flexor carpi radialis (FCR), palmaris longus (PL), flexor digitorum superficialis (FDS) and flexor digitorum profundus (FDP) by stimulation of each quadrant of the electrode, with and without longitudinal or transverse steering currents. Relevant results from these studies are also reproduced in Table I. The thenar and hypothenar eminences and all of the hairy and glabrous surfaces of the digits were left intact, so that a cortical mapping study could still be carried out immediately after these other studies.

For these cortical mapping studies the raccoon was placed in a stereotaxic frame (David Kopf) to provide stability. A craniotomy was performed to allow access to the somatosensory area of the right hemisphere. This oval-shaped craniotomy extended from the frontal sinus anteriorly, to within 5 mm medially of the midline, to a line 20 to 25 mm lateral to the midline and parallel to and just adjacent to the zygomatic arch (requiring bisection and elevation of the temporalis muscle), to about 40 to 60 mm posterior of the bregma. The somatosensory area was centered in this opening, on the third major gyrus back. The dura was reflected to remove it from that region. The stereotaxic frame was rotated to the left so that the opening was roughly horizontal to aid in keeping the cortex moist via repeated lavages with physiological saline. A sketch of the representative cortical landmarks (i.e., blood vessels, sulci, and gyri) was used to record the placement of the recording electrode and for comparison with previous published maps (see electrode placements on Fig. 1, modified from [18]).

B. Recording and Stimulating Techniques

A bipolar surface-recording electrode was constructed from two platinum metal microelectrodes, whose final 1 mm of the recording ends were bent at 90° so that they could lay parallel on the cortical surface, separated by 2 to 4 mm. The electrode was positioned on the surface of the cortex using a Kopf stereotaxic three-axis electrode carrier tilted to be perpendicular to the surface of the cortex. The electrodes were differentially connected to a Grass 511J ac amplifier through a Grass HIP511E high impedance preamplifier. A reference recording ground was clipped to the ear or tongue bar of the stereotaxic frame. Filters were set at 30 to 3000 Hz, with the 60 Hz notch filter engaged. The output of the amplifier was displayed on a Gould digital storage oscilloscope (Model 4162), that could be triggered by the stimulus, and that could plot captured waveforms of interest. The output of the Grass amplifier was fed to an audio amplifier to provide auditory feedback as an aid to localizing the peripheral receptive field of the recording location. This peripheral field was determined by tactile stimulation of the raccoon hand and noted on a diagram of the hand. The receptive field was mapped by listening to the response (or lack of one) produced by gentle stroking of the skin or hairs with the tuff- and/or wooden-end of a Q-tip, or by gentle taps of the Q-tip delivered perpendicular to the surface of the skin.

The stimulation intensity in each cuff quadrant was increased until a repeatable and noticeable short-latency evoked response occurred in the cortex (Table I). The threshold for a movement response was available from the just previously concluded movement studies (also see Table I). Stimulation was increased in a given quadrant until the cortical response saturated. At no time did stimulation exceed 12 ma, even if an evoked response was not seen. Response latencies were determined by inspection of the oscilloscope tracings or printouts from the Gould oscillograph. For data analysis, the cortical receptive field locations were compared with each quadrant's stimulation threshold and with the movement profiles.

At the conclusion of the experiment, the animal was overdosed with pentobarbital, injected intracardially with KCl, and removed from respiratory assist. A detailed postmortem dissection traced the innervation of the median nerve to specific muscles of the paw and forearm. The results of this dissection were then related to the orientation of the nerve branches in the cuff [see Fig. 2(b)] and to the cortical evoked responses [see the Discussion (Section IV)].

III. Results

As expected [19], when the recording electrode was placed within the digit area of the raccoon's somatosensory area, a small circumscribed peripheral receptive field could generally easily be identified on the digits or hand. Stimulation of each quadrant of the cuff electrode array also produced a short latency biphasic response in the digit and/or distal forelimb area of the contralateral somatic sensory cortex, and no response outside of that cortical area. However, the threshold stimulation current needed to produce a cortical evoked potential did vary between quadrants as did the current to produce movement.

Five cortical recording sites were studied in this raccoon (see Fig. 1(b) and Table I). Site #3 was activated from the web region between the digits (see Fig. 3), but also could be activated from the dorsal hairy skin of digits 3, 4, and 5 (suggesting a radial distribution). From the nerve cuff, this site was best activated by stimulation of electrodes at 0 and 270° (both less than 0.1 ma). Threshold activation of this site through the electrodes at 90 and 180° required 6 to 15 times more current to produce an observable response. Fig. 3 compares the responses elicited from each quadrant to a single stimulus pulse of 0.1 ma. This current level was below the movement or muscle activation thresholds of 0.2 ma (0, 90, 180°) and 0.3 ma (270°) (see Table I).

Site #1 was on the gyrus immediately medial to that of site #3. It was activated by light touch to a banana-shaped receptive field that was most sensitive on the lower, lateral part of digit 1 but that continued across the web to the lower medial aspect of digit 2 [see Fig. 4(C)]. Bipolar needle stimulation of lateral digit 1 produced a response with a 14 ms latency [see Fig. 4(C)]. This site was best activated from the nerve cuff by stimulation of electrodes positioned at 90 and 180° where a robust response was produced [Fig. 4(B), with 1 mA stimulation current]. Threshold activation of this site through the electrodes at 0 and 270° required three to five times more current to produce an observable response [Fig. 4(A), produced with a 2 mA stimulation current]. The use of a steering current through the electrode at 180° reduced the threshold for activation of the 0° electrode by 50%.

Site #5, which was on the gyrus anterior to that of site #1 (see Fig. 1), also produced a distinction in orientation responsivity that fell between that shown by Sites #1 or #3. Site #5 was activated by light touch to the medial side of the distal portion of digit 2. From the nerve cuff, this site was best activated by stimulation of electrodes positioned at 0 and 270° (0.2 and 0.1 mA). Threshold activation of this site through the electrodes at 90 and 180° required two to four times more current to produce an observable response (0.5 and 0.7 mA). Site #4 was on the gyrus immediately anterior to that of site #3 and lateral to site #5. A peripheral receptive field could not be found (but recall that part of the palm had been dissected for the tendon studies). For nerve cuff stimulation, this site behaved almost identically to that of site #5.

Recording site #2 was on the gyrus immediately posterior to that of site #1. Electrical stimulation of neither the skin or the cuff produced a response, suggesting that site #2 was posterior to the digit area of somatosensory cortex.

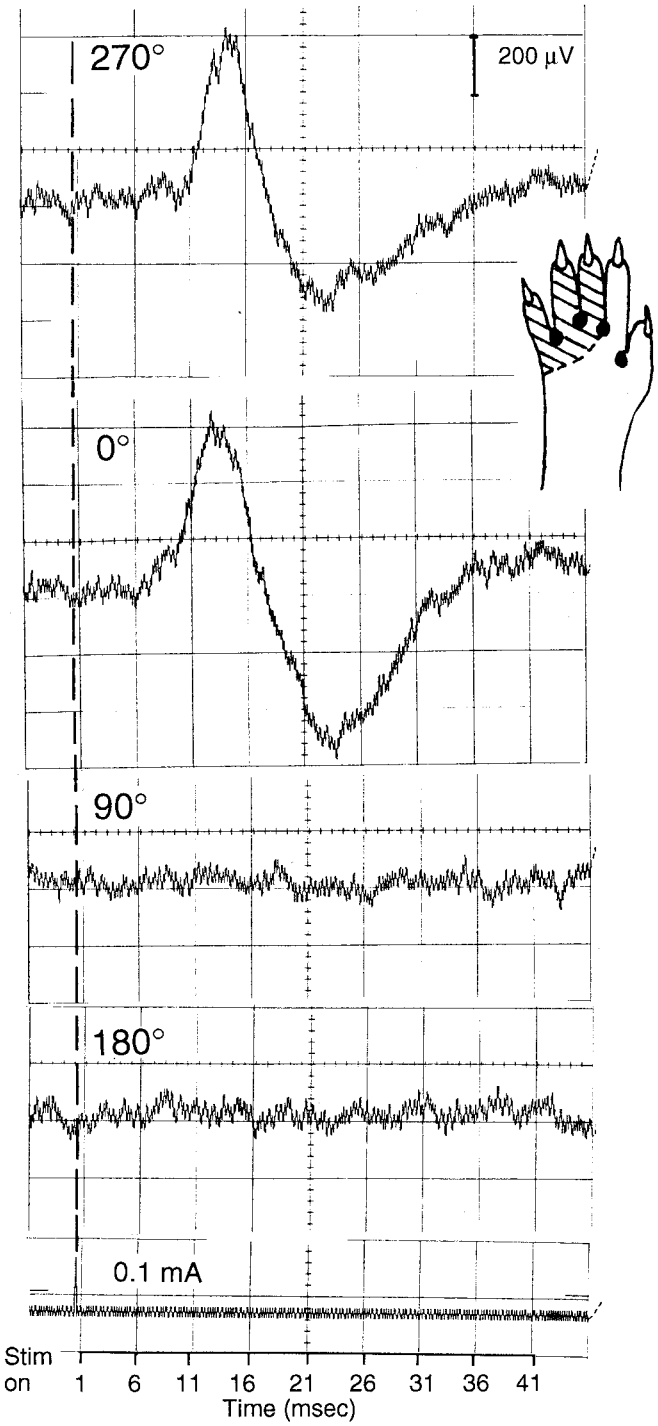


Fig. 3. Comparison of the responses at recording site #3 evoked by electrical stimulation of each quadrant of the cuff electrode with a single 10 μs, 0.1 mA pulse. The receptive field for cortical site #3 was in the webbing between the digits (shown by the black dots on the dorsal view of the paw) and on the hairy skin (shown by diagonal lines) overlying digits 3, 4, and 5.

IV. Discussion

A. Selectivity in Peripheral Somatosensory Neuroprosthetic Coupling

The designer of a sensory neuroprosthesis has a number of options to choose from when considering the optimal location to couple a representation of the sensory signal into that sense's neuronal pathway. Coupling can be made at a peripheral location, at one of the various relay nuclei, or at the cortical level. Tradeoffs include ease of implantation, degree of invasiveness, patient safety, the type and specificity of sensory mapping that occurs at each location, and many other factors. In the neuroprosthetics field, electrical stimulation of sensory afferents for functional restoration currently finds its most accepted clinical application to be its use for cochlear

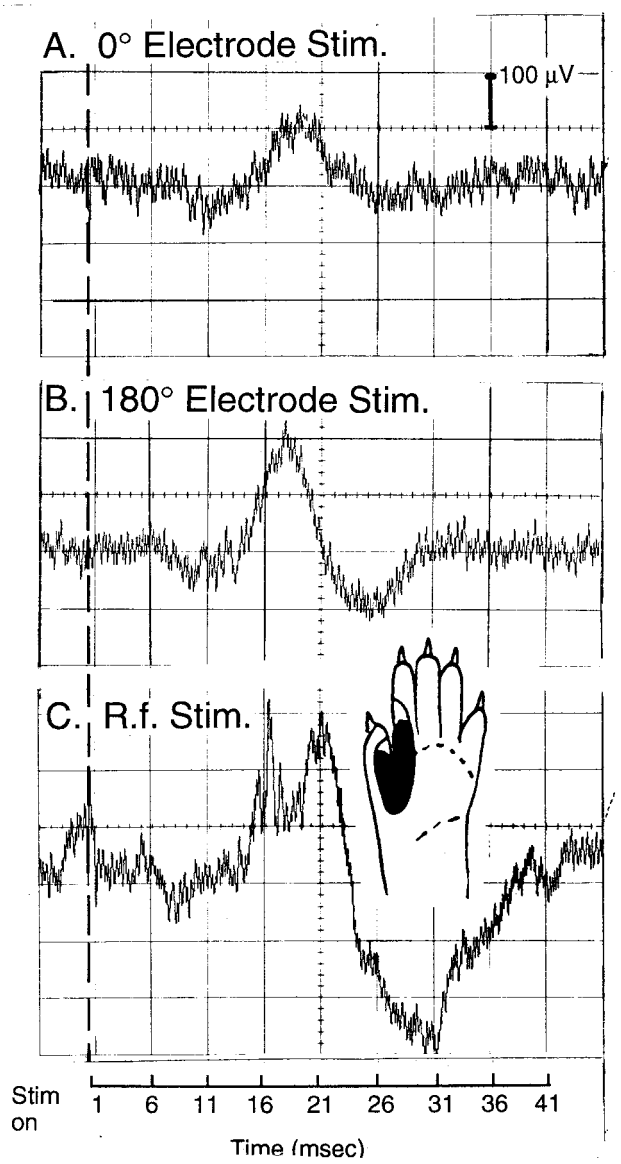


Fig. 4. A comparison of cortical surface responses at recording site #1 evoked by electrical stimulation. Stimulating the 0° quadrant [see Fig. 4(A)] of the cuff electrode required twice the current (2 mA) to produce only half the response amplitude that was produced when the 180° (or 90°) quadrant of the cuff electrode was stimulated at 1 mA [see Fig. 4(B)]. For comparison, Fig. 4(C) illustrates the response to stimulation at 40 mA of the center of the peripheral receptive field by a pair of needle electrodes. The receptive field was centered on the proximal glabrous skin of adjoining areas of digits 1 and 2 (blackened area on the ventral view of the paw), with some activation from more distal parts of lateral digit 1 and medial digit 2.

implants. These implants have been shown to restore functional hearing to some of their recipients, and an awareness of sound to some others.

Neuroprothetics for restoring functional movement have tended to be applied in the periphery, with coupling generally near the motor end plate, on the efferent nerve or at the surface of the overlying skin [4]. Suprathreshold stimulation of the entire nerve itself in this application will excite both the desired efferent fibers to the muscle, the spindle afferents from the muscle, and any A-beta (touch) cutaneous afferents that are in the nerve. Thus, if the nerve is to be the site of coupling, some means of selective activation of a specific fascicle of the nerve bundle or of a specific type of fiber within the bundle needs to be found. To achieve this specificity, a number of individuals have proposed stimulation techniques or electrode designs [3], [5], [6], [9], [11], [12], [14], [19] to activate only a portion of the nerve. We have chosen one of the simplest means of selective activation—that of longitudinal tripolar stimulation by individual quadrants of a 12-electrode spiral nerve cuff assembly [3], [11], [12], [14], [17]. We have also chosen the simplest means of cortical recording—that of a surface evoked potential. Even though we combined both of these simple methods, we were still able to demonstrate movement and evoked somatosensory cortical selectivities, just by activating a different quadrant of the electrode. As more sophisticated nerve coupling schemes become available, and as we employ multi-unit or single-unit neuronal recording techniques, both selectivities should increase to the point where their viability as a motor or sensory prosthesis can be demonstrated.

B. The Raccoon and Somatic Sensation

If selectivity can be demonstrated on the motor (efferent) component, we wondered whether such selectivity also existed on the somatosensory (afferent) side. The raccoon, being one of the consummate animals in terms of manual dexterity, and having such a large and grossly differentiable amount of cortex devoted to the hand and digits [18], seemed to be a natural vehicle for testing this hypothesis. Also the cutaneous domains and the sensory organization of the nerves innervating the raccoon forepaw have been documented [13], as has the motor innervation to its forelimb and hand [16]. The raccoon primary somatosensory cortical area has been well studied [2], [8], [10], [18], [20]. Further, the representation of each digit can be subdivided into glabrous and heterogeneous areas illustrating that afferent projections from the glabrous skin and dorsal hairy skin of each digit are largely segregated at all levels of the raccoon somatosensory system [2], [8].

When comparing the motor and sensory results outlined in Table I with the orientation of the cuff [see Fig. 2(b)], it appears that the receptive fields of the afferent fibers [8] in the raccoon nerve and the efferent fibers [16] to the various muscle groups might well share a topographic relationship of some sort within the nerve. In concept, then, different loci within the digit and hand area of raccoon somatosensory cortex could be activated by stimulating different fascicles of the median nerve. And no activation should be seen at cortical loci outside of the innervation area represented by these nerves.

To fortify this claim, our preliminary observations do demonstrate that selective activation can be achieved at the cortical level. In comparing recording sites #1 and #3, note that the cortical area representing the glabrous skin of digits 1 and 2 (site #1) was activated by cuff stimulation at 90 and 180° while the area representing the hairy skin of the more lateral digits (site #3) was best activated by cuff stimulation at 0 and 270°. This observation is consistent with the positioning of the electrodes (see Fig. 1). One might expect the 0° electrode to have a more radial sensory distribution since the efferents to flexor carpi radialis, carpi radialis and pronator teres lie directly under the 0° electrode and adjacent to the 270° electrode, and were the muscles first activated by stimulation of these two electrodes. Likewise, stimulation of the electrodes at either 90 or 180° produced movement of the wrist and digits at a threshold of 0.2 mA to a 20 Hz pulse train (Table I).

How do raccoon and human forearm innervation patterns compare? Reference [16] provides the anatomical justification for the use of the raccoon, while [13] deals with the pattern of sensory innervation. In [16], we did a detailed mapping of the innervation of the raccoon

forearm, and compared the functional anatomy of the hands and digits with that of the human. While there are substantial differences, the similarities are greater between raccoon and human, than between human and dog or cat. The raccoon does have a divided median nerve in its upper arm in contrast to the single branch in the human. Thus selectivity with a cuff stimulating electrode and a cortical surface recording electrode should be easier to demonstrate in a raccoon than in a human. However, the differences in selectivity should disappear as more selective stimulating electrodes are developed (e.g., [5]), and if a multi-unit, penetrating recording electrode were used rather than a mass-potential, surface one.

Finally, a comment needs to be made regarding the recording of cortical responses under barbiturate anesthesia. Generally the signaling pathway from the somatic periphery to somatosensory cortex is very robust, with cortical neurons able to respond to rapid sequences of peripheral stimuli. Under the deep barbiturate anesthesia that we used, we were unable to entrain the evoked potentials to a 20 Hz train of 6 pulses delivered to the stimulating cuff. In general, the first pulse would evoke a response, followed by barbiturate spindling that seemed to interfere with the responses to subsequent pulses. However, other anesthetic agents used in the study of raccoon cortex, such as alpha-chloralose [2], tend to overemphasize the effects of the somatic input. Again, it would certainly be worthwhile to repeat these experiments with another type of anesthetic.

C. Clinical Utility and Cortical Reorganization

Since the median nerve is a mixed somatic and motor nerve, cuff stimulation can excite both afferent and efferent axons. However, we were able to demonstrate in this raccoon and in two others (unpublished results) that a sensory evoked potential could be produced (at least for one quadrant) at a current level below the level that produced a movement.

The clinical utility of a somatic sensory neuroprosthesis involving a peripheral nerve might best be found in restoring the tactile sense after amputation. If the peripheral nerve were cut by the amputation, movement could not occur due to stimulation. Assuming that the afferent pathways from the nerve stump to the cortical receiving area of the denervated skin remain intact (or latent), then selective stimulation of the nerve above the amputation in theory could be used to provide localized cortical activation. However, since reorganization of the raccoon somatosensory cortical representation occurs following selective digit amputation [7], [20], it is also reasonable to assume that amputation of an entire limb would produce a more profound reorganization, with a concomitant loss of topology in the cortical areas representing the forearm and digits. In an intact animal (i.e., before an amputation), we have shown that selective stimulation of portions of a peripheral nerve can produce localizable and separable responses in the cortex. Thus, there remains for future research two testable conjectures: 1) selective nerve stimulation applied acutely after the amputation, and continued in an appropriate manner, will preserve some elements of a cortical topography; and 2) selective nerve stimulation, applied at a time after amputation where the cortex has already undergone a reorganization, will restore an element of topology to the cortical area. If proven, both of these stimulation paradigms, coupled with the use of appropriate tactile transducers, could help restore some tactile sensitivity following an amputation.

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