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Short communication

# The use of fMRI for determining the topographic organization of cortical fields in human and nonhuman primates

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**Abstract**

In this study, we demonstrate activation of somatosensory cortex in the anesthetized macaque monkey and awake human using fMRI, and confirm the topographic organization of somatosensory cortex previously described in both species. The macaque model provides an efficient means of addressing questions regarding the capabilities and neurophysiological relevance of fMRI, and serves as an interface between established invasive electrophysiological methods in nonhuman primates, and noninvasive imaging assays of functional activation in humans. 

*Keywords:* Macaque; Somatosensory cortex; Topography; Functional magnetic resonance imaging; Anesthesia

The advent of noninvasive imaging techniques in humans, particularly functional magnetic resonance imaging, has led to an avalanche of studies in which investigators seek to localize areas of the brain involved in a variety of perceptual, cognitive, and learning tasks [7,9]. While the questions addressed in these studies are important, and the fMRI technique holds tremendous promise for uncovering the mysteries of the human brain, one very important question regarding this technique has remained unanswered. Can functional magnetic resonance imaging techniques be used to accurately subdivide the neocortex into functional areas, much like electrophysiological recording methods are used in mammals to determine the topographic organization and number of cortical fields within different sensory systems?

In the somatosensory cortex, electrophysiological recording techniques in nonhuman primates have been used to describe the topographic organization of the primary somatosensory field (SI or 3b), as well as adjacent somatosensory fields 3a, 1, and 2 [5,6,8,10,12]. In all of these fields, the topographic organization is similar, with the representation of the foot, hand, and face progressing in a medio-lateral sequence. Similar topographic organization has been demonstrated in the classic electrical stimulation studies in humans by Penfield and Boldrey [11], and recently with noninvasive imaging techniques, such as MEG [15], fMRI [4], and PET [3]. Functional MRI and PET yield a signal based on cortical blood oxygenation level changes. Although they lack the spatial resolution of direct electrophysiological recording techniques, their noninvasive nature and routine use in humans makes them ideal candidates with which to extend our knowledge of sensory cortical organization in humans.

One method for determining the extent to which these techniques can be used to provide detailed information on cortical field organization and number is to use them in combination with electrophysiological recording methods, and compare the results from each. The present investigation is the first step in this process. Our initial question was: Can fMRI be used in monkeys in a manner consistent with its use in humans to determine topographic organization of a cortical field? In this study using a standard fMRI approach on a clinical MR scanner, we examined the activation patterns on the post-central gyrus of anesthetized monkeys resulting from tactile stimulation to different body parts, and compared these patterns of activa-

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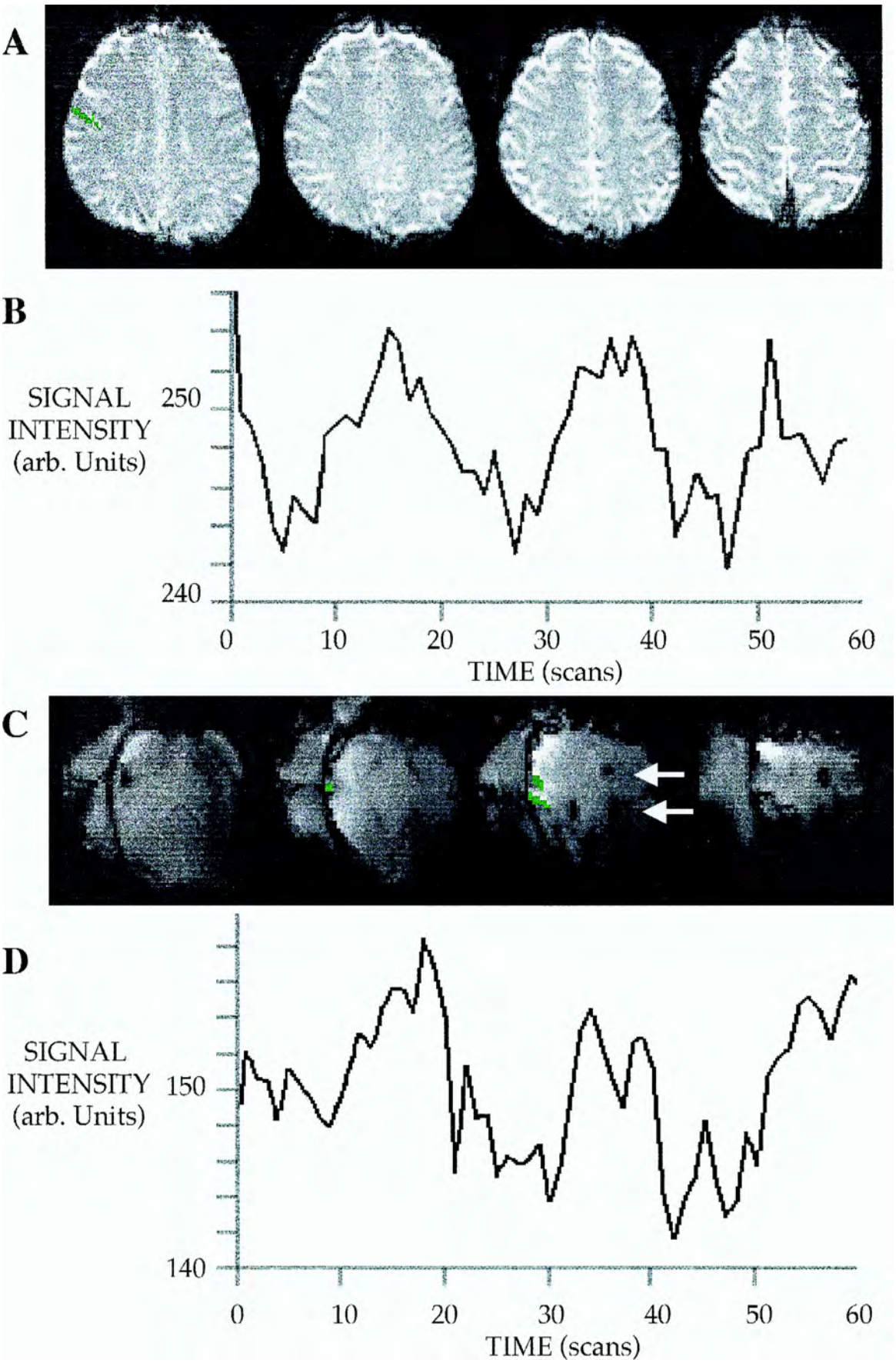
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Fig. 1.

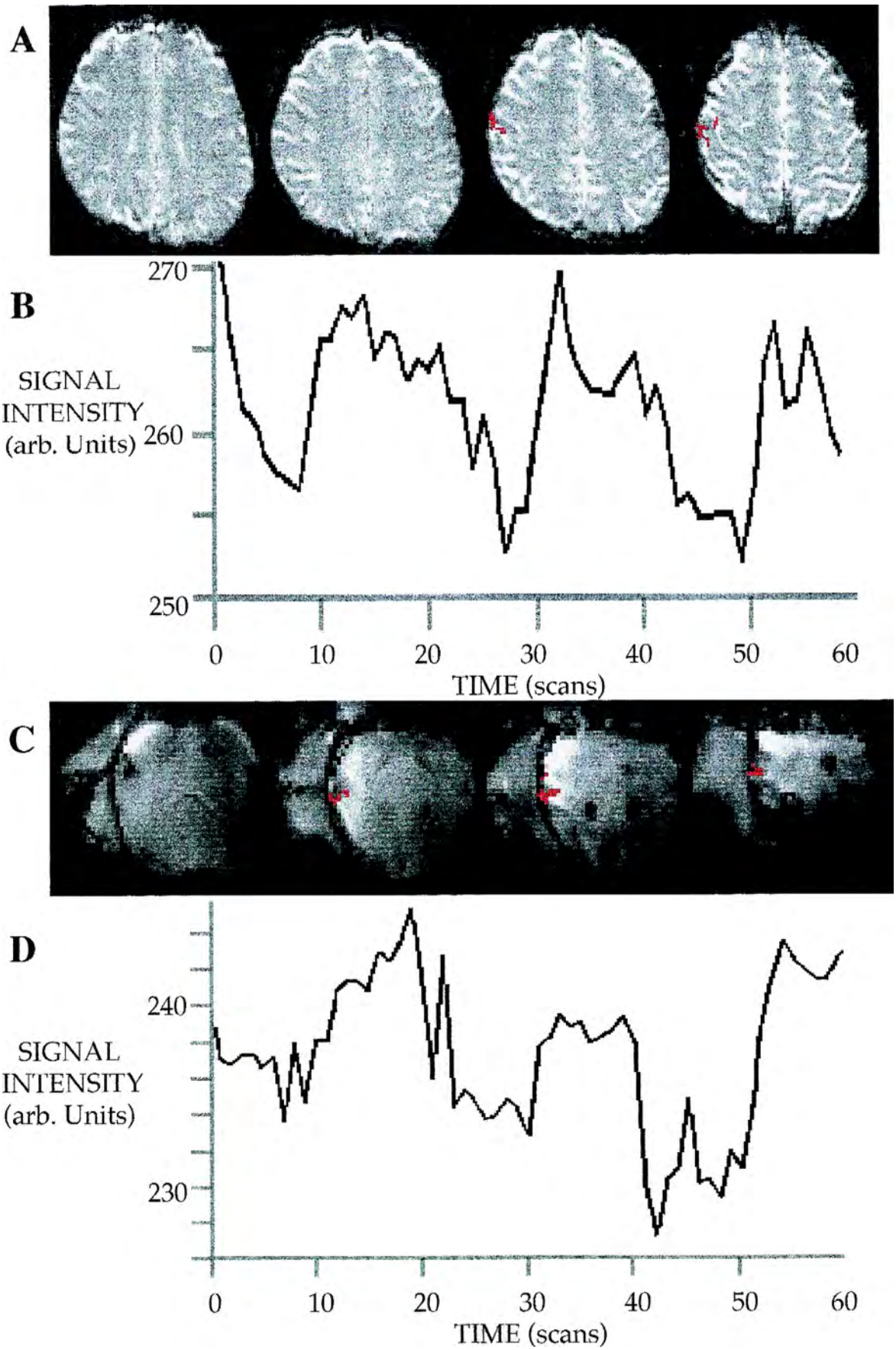
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Fig. 2.

tion with those observed on the post-central gyrus in humans using a similar stimulus. Although fMRI has been shown to be feasible in the awake macaque monkey [2,13], our report is the first to demonstrate successful fMRI in the anesthetized preparation.

In these experiments, two macaque monkeys (*Macaca mulatta*) and one human subject were studied. In the macaque monkeys, small probes were placed rostral and caudal to the post-central gyrus as landmarks. These probes were hollow plastic tubes filled with a dilute gadolinium solution (gadopentetate dimeglumine, Magnevist™, Berlex, NJ). For probe implantation, the animals were initially anesthetized with ketamine hydrochloride (10 mg/kg i.m.). The animals were then intubated and cannulated and maintained on a continuous infusion of lactated Ringers (10 ml/kg/h). Surgical levels of anesthesia were maintained with 1–2% isoflurane. Throughout the experiment, temperature, heart rate, oxygenation level, respiration, and $p_aCO_2$ levels were monitored. The scalp was retracted and two holes were drilled into the skull. The dura was cut and the probes were placed in the brain through the openings. The holes were covered using gelfoam and then sealed with acrylic. The scalp was sutured, and the animal was allowed to recover.

For the fMRI procedures, the methods of animal maintenance and anesthetic induction were identical to those described above. An arterial line was placed in order to closely monitor blood gas concentrations. The animals were artificially ventilated and their $p_aCO_2$ was maintained at 35–45 mmHg. Once the animal was anesthetized, intubated, and cannulated, it was paralyzed with Pancuronium (0.1 mg/kg, i.v.). The level of paralysis was monitored with a train of four electrical pulses administered at a constant voltage to the right wrist using a peripheral nerve stimulator (Digistim II, Neurotechnology, Houston, TX). Blood oxygenation and heart rate were monitored using an MR compatible pulse oximeter (Invivo Research, Orlando, FL). During scanning, the Isoflurane level was reduced to 0.6%. When scanning was complete, paralysis was reversed using Atropine (0.1 mg/kg, i.v.) followed by Edrophonium (0.5 mg/kg, i.v.). A similar anesthetic protocol has been used successfully in humans during fMRI [1]. All procedures on humans were approved by the Human Subjects Committee at UC Davis, and the Committee of Human Research at UC San Francisco. The procedures on macaque monkeys were approved by the Animal Use and Care Administrative Advisory Committee at UC Davis, and the Committee on Animal Research, UC San Francisco.

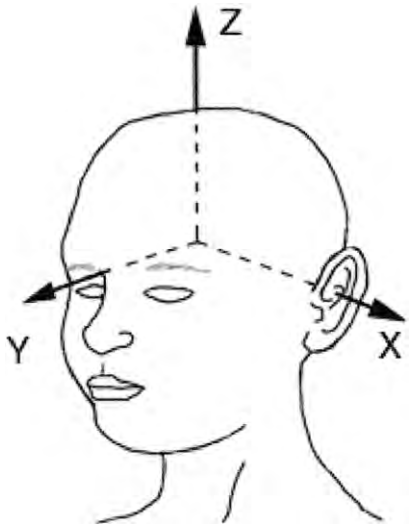


Fig. 3. Diagram of the three planes with respect to the head. In the text, Z is referred to as superior–inferior, X is referred to as medial–lateral, and Y is referred to as anterior–posterior.

Functional magnetic resonance imaging was performed using a GE Signa 1.5T system (GE Medical Systems, Milwaukee, WI). The spectrometer was equipped with 5.6 operating software, and the sr120 gradient system allows for routine echo planar imaging capability. Twenty-second periods of activation were interleaved with similar periods of rest. For the human subject, axial multi-slice gradient recalled echo planar images (GR-EPI) were acquired with the following parameters: TR = 2 s, TE = 69 ms, field-of-view: 40 cm × 20 cm (matrix 256 × 128), slice thickness = 6 mm, inter-slice interval = 0.5 mm, six slices from the vertex to the Sylvian fissure. Six alternating blocks were used, for a total time of 2 min. Thus, a total of 10 multi-slice image sets were acquired per rest/activation

Fig. 1. Cortical activation resulting from stimulation of the lips on the left side of the face in the human (A) and monkey (C). A and C show four consecutive axial EPI slices from the brain (slice 1 = ventral, top = rostral). Data was not superimposed on to a high resolution image. Active voxels are shown in green. The graphs in B and D depict the average change in signal intensity over time of the active voxels from 1A and C, respectively. In C, the white arrow indicates the location of the fluid-filled probes placed in the cortex prior to scanning.

Fig. 2. Cortical activation resulting from stimulation of the left hand in the human (A) and monkey (C). A and C show four consecutive axial EPI slices of the brain (slice 1 = ventral, top = rostral). Active voxels are shown in red. The average change in signal intensity over time is illustrated in B and D for the active voxels in 2A and C, respectively. Note that the location of the activation is in the more dorsal slices than in Fig. 1 (see also Fig. 4).

Fig. 4. Additional demonstration of the location and reproducibility of the hand and face representations. A and B show consecutive axial EPI images of activation in response to stimulation of the hand (red, A) and the face of the monkey (green, B). These images were taken from the same monkey that is depicted in Figs. 1 and 2. C and D are two examples of face stimulation from the second monkey taken during the same scanning session. Activation on the first (most inferior) slice is located in the second somatosensory cortex. Conventions as in previous figures.

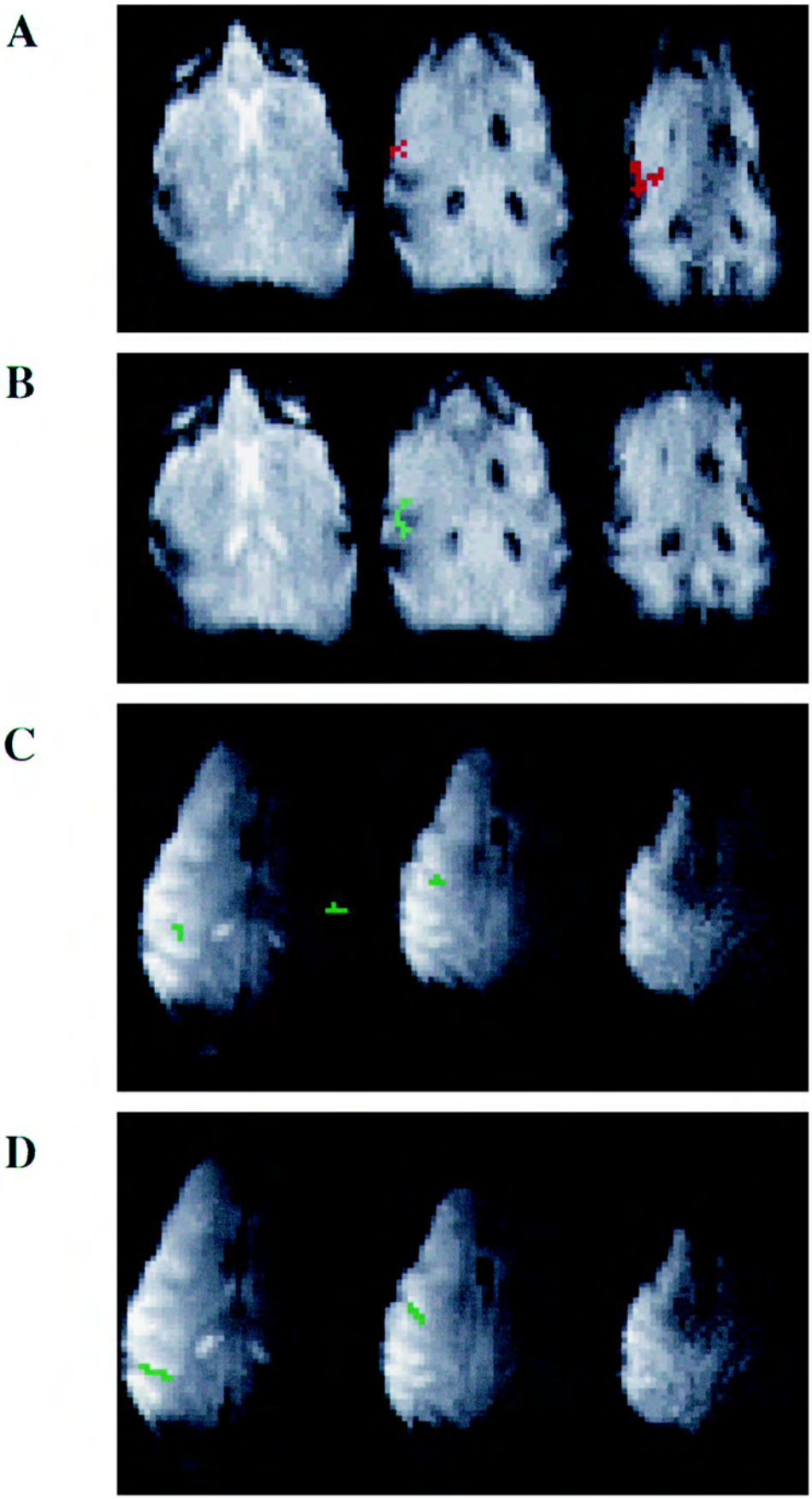


Fig. 4.

block. For the monkey subjects, similar axial multi-slice GR-EPI were acquired, but with the following parameters: TR = 2.5 s, TE = 69 ms, field-of-view: 40 cm × 20 cm (matrix 256 × 128), slice thickness = 4 mm, inter-slice interval = 0.5 mm, five slices. Using these parameters, a total of eight multi-slice image sets were acquired per 20-second rest/activation block with a total scan time of 3 min.

The human and monkeys were supine during scanning. The human's head was held in place with a plastic pillow (Olympic Vac-Pac, Olympic Medical, Seattle, WA) filled with styrofoam packing beads, which was fitted around the head. The air was removed from the pillow so that it became rigid and conformed to the contours of the head. The subject was instructed to remain still with eyes closed during each scan. The head of the monkey was centered in the coil and packed tightly into the standard GE head holder using towels of various sizes. It was then taped securely to the head holder across the forehead, under the chin and across the shoulders. Movement of the human and monkeys during scanning was minimal based on an assessment of the location in X, Y, and Z (Fig. 3) of the center of mass over time.

Two types of painless somatosensory stimuli were used. In the monkey, a sponge was applied to the lips and hand, and in the monkey and human, a calibrated cutaneous stimulus was applied to the lips and hand. The left side of the body was stimulated in both human and nonhuman subjects because one monkey was missing a distal digit tip on the right hand. In the monkeys, tactile stimulation of the lips was administered with a sponge which was moved from the midline to the corner of the mouth and back at approximately 1 Hz. Similarly, a sponge was moved across the hand from the wrist, across the dorsal palm to the tips of the fingers at approximately 1 Hz. For the human, a sponge was used to brush the lips and the distal tips of D2 and D3 in a similar fashion.

In order to assess reproducibility, a calibrated painless somatosensory stimulus was administered to the monkeys. Pneumatically driven mechanical taps were applied (Somatosensory Stimulus Generator; BTi, San Diego, CA) either to the lips and tongue or to the palm and distal digit tips. Four stimulus channels were used, each ending in a stimulus bladder with a 1-cm diameter driven at a pressure of 25 psi. For stimulation of the face, one bladder was placed on the left side (L) of each lip and two were placed on the left side of the tongue. For the hand, one bladder was placed on distal LD1 and one on LD2 and two were placed on the palm at the base of LD1 and LD2. During the 20-second stimulation blocks, the cutaneous stimulus was applied at 2 Hz.

Data analysis and display were performed using the Stimulate software package [14] on a Sun Ultra 1 Sparc workstation (Sun Microsystems, Mountain View, CA). Cross-correlation analysis was used to determine significantly active voxels. A correlation threshold of $r = 0.3$ was used with a cluster threshold of three voxels. The active voxel number and the center of mass were calculated for both face and hand activation and compared using a paired *t*-test.

Somatosensory stimulation of the lips of the human volunteer gave rise to a pattern of activated pixels immediately posterior to the central sulcus, on the post-central gyrus (Fig. 1A). In the monkey, stimulation of the lips resulted in activation between the implanted probes on the post-central gyrus, just caudal to the central sulcus and superior to the lateral sulcus (Fig. 1C). Similarly, in both the monkeys and human, stimulation of the hand resulted in activation caudal to the central sulcus and superior to the activation resulting from face stimulation (Fig. 2A and C).

To analyze the locations of activation in the monkey, the five trials from a single monkey in which both the face and hand were stimulated in the same scanning session, were examined. Because the head and scan locations were constant within a trial, the center of mass and extent of activation could be compared for the two stimulus conditions. The location of the face and hand activation were significantly different in the superior–inferior plane (Z, Fig. 3; $p = 0.01$). The hand representation was an average of 12.4 mm superior (hand S.D. = 5.4 mm, face S.D. = 2.0 mm) to that of the face. They were also significantly different in the medial–lateral plane (X, Fig. 3; $p = 0.04$) with the center of the hand representation being an average of 10.0 mm (hand S.D. = 7.8 mm, face S.D. = 11 mm) medial to that of the face. In the anterior–posterior plane (Y, Fig. 3), there was no significant difference between the location of the hand vs. face representation, although the face was an average of 11.2 mm anterior to that of the hand. In this dimension, the standard deviation was quite large (hand S.D. = 43.2 mm, face S.D. = 25.8 mm).

In the monkey, the extent of activation was consistent across trials for the calibrated stimulus (Fig. 3). For the cutaneous stimulation of the face, the mean in plane extent of activation was 65.7 $mm^2$ (S.D. = 20.7 $mm^2$). The mean extent of activation for the hand was 69.3 $mm^2$ (S.D. = 41.4 $mm^2$). The mean increase in blood oxygenation level-dependent signal during stimulation of the face and hand was approximately 4% in the human and 3% in the anesthetized monkey (Fig. 1B and D, Fig. 2B and D).

Thus, comparison of the face and hand activation shows that the face representation is inferior and lateral to the location of activation produced by stimulating the hand (Fig. 1C, Fig. 2C, and Fig. 4A and B). It can be demonstrated that the somatotopic organization of the post-central gyrus is similar in both species. The topographic pattern of activation on the post-central gyrus in humans is not surprising, since a similar organization has been demonstrated using both invasive and noninvasive techniques [3,4,11,15]. The interesting result is that we demonstrate that it is possible to observe blood oxygenation level-dependent signal changes using fMRI in the anesthetized

macaque monkey. The topographic pattern of activation observed for the monkey corresponds well to electrophysiological recording results in monkeys, which demonstrate a medio-lateral relationship between representations of the hand and face, respectively, consistent with that observed in the present investigation.

The differences in anesthetic state in the monkeys and human in the present investigation does not bear on the interpretation of our results. Comparisons between activation patterns generated with tactile stimulation in anesthetized and unanesthetized humans demonstrate that only the number of voxels activated between the two conditions changes (a 15% decrease with 0.6% isoflurane), while the spatial location of the activity remains constant [1].

This preparation for measuring brain function opens the door to several intriguing possibilities regarding the capabilities of the fMRI method, and the elucidation of the organization of the neocortex. Specifically, this study represents the first step in relating the fMRI-observed signal changes to established electrophysiological measures, by demonstrating fMRI in a model appropriate for post-hoc invasive investigation. By aligning the visualized probes in both procedures, we can compare the maps generated using fMRI and electrophysiological recording techniques under conditions in which the stimuli are identical. Thus, the detailed information that can be obtained using invasive techniques in monkeys can be more readily extrapolated to the human condition, and work done in humans can be readily compared to monkeys. The overall goal is to determine which features of organization are the same across primates, and examine these in more detail in nonhuman primate models.

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## References

[1] J.F. Antognini, M. Buonocore, E.A. Disbrow, E. Carstens, Isoflurane anesthesia blunts cerebral responses to noxious and innocuous stimuli: a fMRI study, Life Sci. 61 (1997) 349–354.
[2] D.J. Dubowitz, D.Y. Chen, D.J. Atkinson, K.L. Grieve, B. Gillikin, W.G. Bradley Jr., R.A. Andersen, Functional magnetic resonance imaging in macaque cortex, Neuroreport 9 (1998) 2213–2218.
[3] P.T. Fox, H. Burton, M.E. Raichle, Mapping human somatosensory cortex with positron emission tomography, J. Neurosurg. 67 (1987) 34–43.
[4] T.A. Hammeke, F.Z. Yetkin, W.M. Mueller, G.L. Morris, V.M. Haughton, S.M. Rao, J.R. Binder, Functional magnetic resonance imaging of somatosensory stimulation, Neurosurgery 35 (1994) 677–681.
[5] K.J. Huffman, L. Krubitzer, J. Clarey, R. Tweedale, The topographic organization of area 3a in the marmoset monkey (*Callithrix jacchus*), Soc. Neurosci. Abstr. 22 (1996) 107.
[6] J.H. Kaas, R.J. Nelson, M. Sur, C.-S. Lin, M.M. Merzenich, Multiple representations of the body within the primary somatosensory cortex of primates, Science 204 (1979) 521–523.
[7] K.K. Kwong, J.W. Belliveau, D.A. Chesler, I.E. Goldberg, R.M. Weisskoff, B.P. Poncelet, D.N. Kennedy, B.E. Hoppel, M.S. Cohen, R. Turner, H.-M. Cheng, R.J. Brady, B.R. Rosen, Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation, Proc. Natl. Acad. Sci. USA 89 (1992) 5675–5679.
[8] M.M. Merzenich, J.H. Kaas, M. Sur, C.-S. Lin, Double representation of the body surface within cytoarchitectonic areas 3b and 1 in 'SI' in the owl monkey (*Aotus trivirgatus*), J. Comp. Neurol. 181 (1978) 41–74.
[9] M.E. Mosely, G. Glover, Functional MR imaging. Capabilities and limitations, in: J. Kucharzyk, M.E. Moseley, T.P.L. Roberts, W.W. Orrison, Jr. (Eds.), Neuroimaging Clinics of North America, Vol. 5, W.B. Saunders, Philadelphia, 1995, pp. 161–191.
[10] R.J. Nelson, M. Sur, D.J. Felleman, H. Kaas, Representations of the body surface in postcentral parietal cortex of *Macaca fascicularis*, J. Comp. Neurol. 192 (1980) 611–643.
[11] W. Penfield, E. Boldrey, Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation, Brain 60 (1937) 389–443.
[12] T.P. Pons, P.E. Garraghty, C.G. Cusick, J.H. Kaas, The somatotopic organization of area 2 in macaque monkeys, J. Comp. Neurol. 241 (1985) 445–466.
[13] L. Stefanacci, P. Reber, J. Costanza, E. Wong, R. Buxton, S. Zola, L. Squire, T. Albright, fMRI of monkey visual cortex, Neuron 20 (1998) 1051–1057.
[14] J.P. Strupp, Stimulate: a GUI based fMRI analysis software package, Neuroimage 3 (1996) S607.
[15] T.T. Yang, C.C. Gallen, B.J. Schwartz, F.E. Bloom, Noninvasive somatosensory homunculus mapping in humans by using a large-array biomagnetometer, Proc. Natl. Acad. Sci. USA 90 (1993) 3098–3102.