Evidence for Interhemispheric Processing of Inputs From the Hands in Human S2 and PV

ELIZABETH DISBROW,[1,3] TIM ROBERTS,[3] DAVID POEPPEL,[4] AND LEAH KRUBITZER[2]
[1]*Department of Neurology and* [2]*Department of Psychology, Center for Neuroscience, University of California, Davis 95616;* [3]*Biomagnetic Imaging Laboratory, Department of Radiology, University of California, San Francisco, California 94143-0628; and* [4]*Department of Linguistics and Department of Biology, University of Maryland at College Park, College Park, Maryland 20742*

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Disbrow, Elizabeth, Tim Roberts, David Poeppel, and Leah Krubitzer. Evidence for interhemispheric processing of inputs from the hands in human S2 and PV. *J Neurophysiol* 85: 2236–2244, 2001. In the present investigation, we identified cortical areas involved in the integration of bimanual inputs in human somatosensory cortex. Using functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG), we compared the responses to unilateral versus bilateral stimulation in anterior parietal cortex and areas in the Sylvian fissure of the contralateral hemisphere. The extent of fMRI activation on the upper bank of the Sylvian fissure, in the second somatosensory (S2) and the parietal ventral (PV) areas, was significantly larger for bilateral stimulation than for unilateral stimulation. Using MEG, we were able to describe the latency of response in S1 and S2/PV to unilateral and bilateral stimulation. The MEG response had three components under both stimulus conditions. An early peak in S1 at 40 ms, a middle peak in S2/PV at 80–160 ms, and three late peaks in S2/PV at 250–420 ms. There was an increase in magnetic field strength in S2/PV to bilateral stimulation at 300–400 ms post stimulus. The fMRI results indicate that, as in monkeys, S2/PV receives inputs from both the contralateral and ipsilateral hand. The MEG data suggest that information is processed serially from S1 to S2. The very late response in S2/PV indicates that extensive intrahemispheric processing occurs before information is transferred to the opposite hemisphere. The neural substrate for the increased activation and field strength at long latencies during bilateral stimulation can be accounted for in three ways. Under bilateral stimulus conditions, more neurons may be active, neuronal firing rate may increase, and/or neural activity may be more synchronous.

INTRODUCTION

A unique behavior exhibited by humans is their ability to manipulate the physical environment with their hands. Yet relatively little is known in humans about the areas of the neocortex involved in complex behaviors such as tactile discrimination and recognition, manual dexterity, and bilateral coordination of the hands. To understand complex behavior such as bilateral coordination of the hands, it is important to examine where such information is processed and how these regions are organized and interconnected. One of the requisites for these behaviors is the integration of inputs across the hand and between hands. We define integration as the combination of the inputs from different neurons with discrete receptive fields across the surface of the skin. For example, cortical regions involved in the discrimination of object size and shape must access inputs from different locations of one hand, such as various portions of several digits. For tasks involving both hands, inputs from both topographically matched and mismatched locations of both hands must ultimately be combined.

In nonhuman primates, our understanding of cortical areas involved in integrating inputs across or between the hands has increased substantially. Neurons in areas in posterior parietal cortex and the lateral sulcus have large receptive fields that encompass much larger skin surface areas of the hand than receptive fields for neurons in areas 3b or 1 (i.e., compare Nelson et al. 1980 with Krubitzer et al. 1995; Whitsel et al. 1969). While the existence of neurons with bilateral receptive fields on the hands has been shown in several somatosensory cortical areas including areas 2 and 5 (Iwamura 1999; Iwamura et al. 1994), area 7b (Dong et al. 1994; Robinson and Burton 1980a), and the second somatosensory area (S2) (Robinson and Burton 1980a,b; Whitsel et al. 1969), they are most common in S2, where their incidence is reported to be as high as 90% (Whitsel et al. 1969). Cortical fields in the lateral sulcus and insula other than S2 have been described in nonhuman primates (Cusick et al. 1989; Krubitzer et al. 1995; Robinson and Burton 1980a,b), but the number, extent, and internal organization of these fields have not been completely characterized.

Similarly in humans, the number, extent and internal organization of fields on the upper bank of the lateral sulcus, or Sylvian fissure, have not been completely described. As in other primates (Burton et al. 1995; Krubitzer and Kaas 1990; Krubitzer et al. 1995), humans have an S2 and a parietal ventral area (PV; probably analogous to SIIc and SIIr, respectively, of Whitsel et al. 1969), which each contain a topographically organized representation of cutaneous receptors (Disbrow et al. 2000). These two areas are mirror symmetric representations of the body's surface that are joined at the representations of the hands, feet, and face, and flanked by more proximal body part representations (Fig. 1). As in nonhuman primates, there appears to be a number of additional cortical fields along the upper bank of the Sylvian fissure that are differentially active

Address for reprint requests: E. Disbrow, Dept. of Neurology, UC Davis Center for Neuroscience, 1544 Newton Ct., Davis, CA 95616 (E-mail: elizabeth.disbrow@radiology.ucsf.edu).

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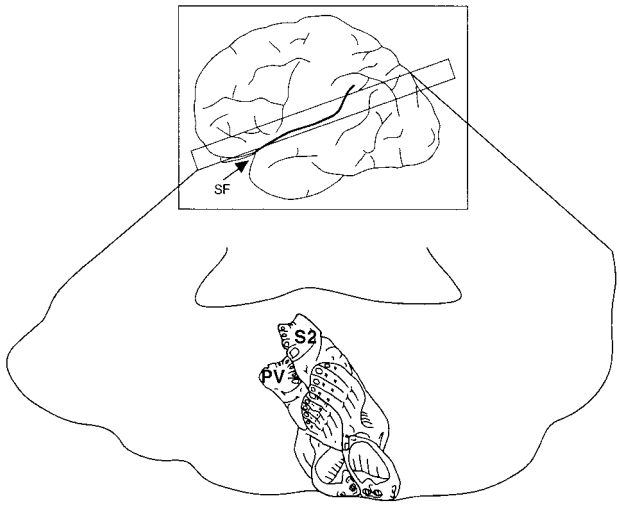

FIG. 1. The second somatosensory area (S2) and parietal ventral area (PV) homunculi displayed on an axial drawing of the left hemisphere. The figure of the whole brain indicates the location of the axial drawing with respect to the Sylvian fissure (SF). Rostral is to the left and lateral is to the bottom of the axial drawing.

under a number of different stimulus conditions. Burton et al. (1993) suggested two areas of activation along the parietal operculum and insula. Further, they have described two foci of activation on the parietal operculum in response to cutaneous versus deep stimulation (Burton et al. 1997). Ledberg et al. (1995) described differential activation in cortex of the Sylvian fissure in response to microgeometric versus macrogeometric tactile stimuli. Recently we described two fields, in addition to S2 and PV, on the upper bank of the Sylvian fissure, one rostral to PV that we termed the rostral lateral area (RL), and one caudal to S2 that is in the location of area 7b in nonhuman primates (Disbrow et al. 2000). However, whether these areas are involved in integrating inputs from the hands is not known.

The present series of studies combine functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) techniques to address two questions. First, where in the human Sylvian fissure are bimanual inputs processed? More specifically, are the somatosensory areas described in the preceding text activated differentially by stimulation of one hand versus both hands? The use of fMRI is ideal for addressing this question because it provides high spatial resolution. Second, when are bimanual inputs processed in the human Sylvian fissure? That is, what is the temporal pattern of activation of cortical somatosensory areas? Although cortical connections cannot be directly studied in humans, MEG has high temporal resolution allowing us to make inferences about connectivity within and between hemispheres.

METHODS

fMRI

All studies were performed with the approval of the institutional human studies committee. Twelve healthy subjects (5 men, 7 women, all right handed, aged 25–50 yr) provided informed consent before participating in the study. Imaging was performed using a standard clinical GE 1.5 Tesla scanner. Two radio frequency coils were used, a whole head coil, and a 3-in surface coil (GE Medical Systems, Milwaukee, WI). A single coil was used for each subject. We initially used the 3-in surface coil because of the superior signal-to-noise ratio. However, the difference in activation patterns appeared to be negligible and not worth losing the ability to collect data from both hemispheres offered by the whole head coil.

First, an anatomical high-resolution three-dimensional SPGR (3-dimensional steady precession gradient-recalled) series (acquisition: axial, interleaved, 256 × 256 matrix, FOV 40 × 40; 124 slices, 1-mm slice thickness, repetition time = 35 ms, echo time = 6 ms, flip angle = 30°, 1 NEX, fatsat) was collected for the determination of Talairach coordinates. Then an ultrafast echo planar gradient echo imaging sequence designed to detect variations in local T_2^* (repetition time = 2 s, echo time = 60 ms, flip angle = 60°) was used. For both coils a 256 × 128 matrix was used with a field of view of 40 × 20 cm, a slice thickness of 5 mm (0.5-mm gap) and thus a voxel (3-dimensional pixel) size of 1.56 × 1.56 × 5 mm.

A single fMRI scan (1 stimulus condition) lasted 2 min, 20 s, during which a total of 70 repetitions of the brain image (5–7 slices) were collected. The brain was scanned from just above the lateral ventricles to the middle temporal sulcus, and the number of slices collected was based on the size of the subject's head. Each imaging sequence consisted of alternating 20-s intervals of stimulation (either uni- or bilateral) and rest.

Stimuli were presented using Semmes-Weinstein monofilaments (Stolting, Wood Dale, IL). Stimulation was applied to the right or right and left thumb, palm, and index finger. A monofilament with a 0.71-mm diam, which exerted a force of 0.74 N was moved across the stimulus area(s). At the beginning of a stimulus period, the filament was placed in contact with the thumb of the subject. The filament was dragged across the skin, down the thumb to above the wrist, across the palm to the tip of the index finger, back down the index finger and over to the tip of the thumb. This stimulus pattern was repeated at 0.3 Hz for the duration of the 20-s stimulus period. For bilateral stimulation, two investigators administered the stimuli to matched locations on each hand.

During scanning, each subject's head was held in position with a plastic pillow (Olympic Vac-Pac, Olympic Medical, Seattle, WA) filled with Styrofoam packing beads. The air was removed from the pillow so that it became rigid and conformed to the contours of the head. Subjects were instructed to remain still, keeping their eyes closed during each scan.

Data analysis and display were done using Stimulate (Strupp 1996). Cross-correlation analysis was used to determine significantly active voxels. A correlation threshold of $r = 0.3$ (alpha level of $P < 0.02$) was used with an in-plane cluster threshold of four voxels. Patterns of activation were superimposed on to high resolution three-dimensional images. The centroid of the S2/PV activation was calculated, and the standardized stereotaxic coordinates of the centroids were determined (Talairach and Tournoux 1993). These coordinates were then compared within subjects, using a paired-*t*-test, to determine if there was a significant difference for the location of activation of S2/PV for the uni- versus bilateral stimulus conditions.

MEG

Twelve subjects (8 men, 4 women, all right handed, aged 25–50 yr; not the same subjects used for the fMRI study) provided informed consent before participating. In all subjects, data were acquired from the left hemisphere during stimulation of the right index finger as well as the right and left index fingers. Pneumatically driven mechanical taps (25 lbs/in^2) were applied to the distal fingertips of subjects' index fingers with a balloon diaphragm with a 1-cm diam. Due to technical constraints, this stimulator could not be used for the fMRI experiments. Stimulus duration was 30 ms; interstimulus interval was pseudo randomly varied from 3.5 to 4.5 s. In each of the conditions, stimuli were repeated 200–250 times.

Neuromagnetic fields were recorded in a shielded room using a 37-channel biomagnetometer system (Magnes, BTi, San Diego, CA). The 37 first-order gradiometers are arranged in a concentric radial

distribution over a concave surface with an intercoil separation of 2.2 cm and an angular field of view of ~70°. The diameter of the sensor array head is 14 cm. Epochs of 500-ms duration (plus 100-ms prestimulus) were acquired with a 1.0-Hz high-pass cutoff and a sampling rate of 1 kHz. The sensor array was positioned over somatosensory cortex. The sensor was initially optimized for recording early S1 responses (central-parietal) and subsequently moved to a more lateral and anterior position to better record from the S2/PV area of the lateral sulcus (central-temporal).

Epoch data that were time locked to stimulus onset were averaged and band-pass filtered (8–40 Hz) before additional analysis. Parameters that were evaluated as a function of uni- or bimanual stimulation include the amplitude of the evoked response, and root mean square activity across channels (RMS). The position, orientation, and strength of the estimated dipoles was computed using a single equivalent current dipole model (Hämäliänen 1993). An anatomic reference frame was established using a digital sensor position indicator. Receivers were used to triangulate the signal from the indicator placed at fiducial reference points on the subject's head surface, such as the nasion, left and right preauricular points. These points were used to define the MEG reference frame in which the source localization was described. Radiological identification of these fiducials on high resolution MRI allowed for the transformation of MEG space into the anatomic (MRI) coordinate system and the anatomical registration of the MEG sources. The computed dipoles were co-registered to individual subjects' MR images (3-dimensional SPGR sequence, TR/TE/Flip angle = 35 ms/6 ms/30°, 1-mm spatial resolution) to determine their location in an anatomic context.

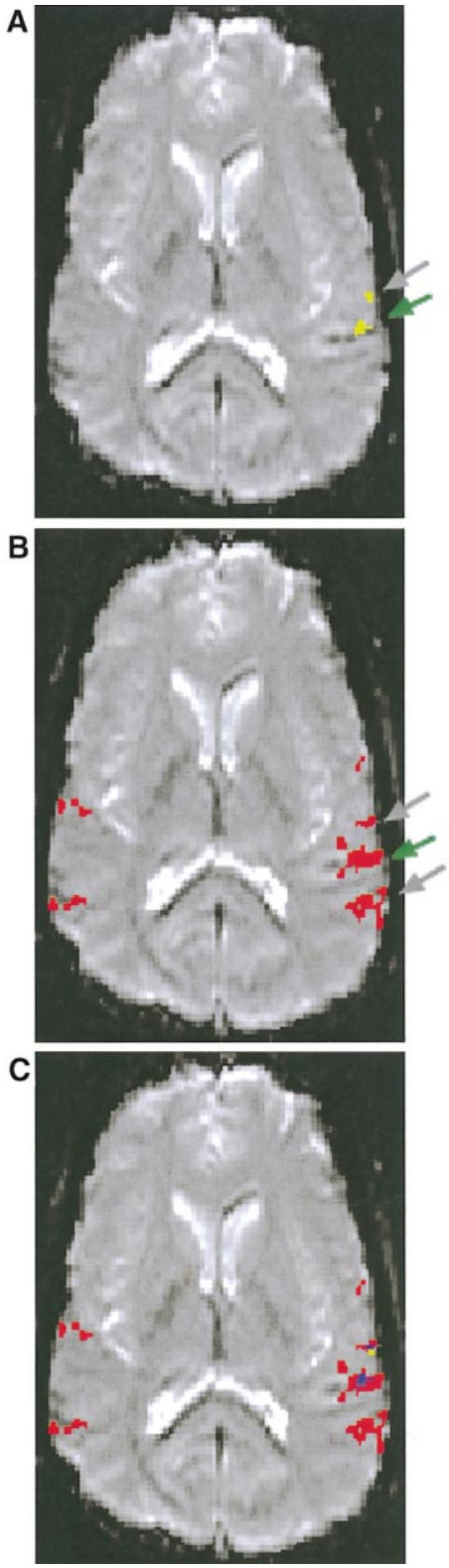

FIG. 2. Three axial echo planar images taken at the same slice location under various stimulus conditions. The image contains the upper bank of the lateral sulcus. Rostral is to the top, lateral to the right and left of midline. *A*: yellow voxels were significantly active during stimulation of 1 hand. Green arrow indicates the contralateral hand representation in S2 and PV. Gray arrow indicates the contralateral rostral lateral area (RL). *B*: red voxels indicate regions that were significantly active during stimulation of both hands. The activation in the hand representation in S2 and PV for bilateral stimulation (green arrow) is larger than in the unilateral stimulus condition. Rostral gray arrow indicates RL and caudal gray arrow indicates 7b. *C*: overlap of the uni- and bilateral activation patterns from *A* and *B*. Those voxels that were active in both conditions are blue. Thus cortex responding only to unilateral stimulation is yellow and blue, and cortex responding to bilateral stimulation is red and blue. Notice that in this subject 7b is only active during bilateral stimulation.

RESULTS

fMRI

Unilateral and bilateral stimulation of the hand resulted in significant activation in 3 separate locations on the upper bank of the Sylvian fissure in all subjects (Fig. 2). Results are reported for the hemisphere contralateral to unilateral stimulation unless otherwise indicated. A large central focus (Fig. 2, *A* and *B*, green arrow) was consistently activated under both stimulus conditions and corresponds to S2 and PV. The Talairach coordinates of S2 and PV in the present study (Table 2), conform to those in a previous study in which the topographic organization of these fields was described in detail (Disbrow et al. 2000). S2 and PV each contain complete representations of the body's surface that are organized as mirror symmetric maps, joined at the representations of the hands, feet, and face (Fig. 1). Thus although two separate cortical fields are located in this region, only one focus of activation can be discerned in response to stimulation of the hand. For this reason, we refer to these two fields in this study as S2/PV.

Stimulation of the hand resulted in activation in two additional locations in the lateral sulcus that have been previously described in humans (Fig. 2*B*). An area rostral to PV termed the rostral lateral area (RL; Fig. 2, *A* and *B*, rostral gray arrow) was activated in 7 of the 12 subjects in each of the stimulus conditions (Table 1). A third focus, caudal to S2 was in the location of 7b (Fig. 2*B*, caudal gray arrow). 7b was activated in

TABLE 1. *A record of cortical activation, as measured using fMRI, for all 12 subjects*

	Unilateral			Bilateral		
Subject	RL	S2/PV	7b	RL	S2/PV	7b
DMS	X	X		X	X	
SB	X	X	X	X	X	X
LM		X			X	
PF		X			X	
TB	X	X			X	X
LK	X	X		X	X	X
HR	X	X		X	X	
RT		X	X		X	X
VC	X	X		X	X	
PS		X		X	X	
SS	X	X		X	X	X
KA	X	X		X	X	
Total	8/12	12/12	2/12	8/12	12/12	5/12

fMRI, functional magnetic resonance imaging; RL, rostral lateral area; S2, second somatosensory area; PV, parietal ventral area. X, significant activation in the indicated region.

2 of 12 subjects in the unilateral stimulus condition and 5 of 12 subjects in the bilateral condition. The locations of the centroids of activation were not significantly different for the two conditions. The mean Talairach coordinates of the hand representations for S2 and PV, RL, and 7b are listed in Table 2, and conform to those described in a previous study of these regions (Disbrow et al. 2000).

Comparisons of the extent of activation for the uni- and bilateral stimulation conditions were made for S2 and PV, RL, and 7b. In S2 and PV, there was an increase in the extent of activation during bilateral stimulation, while such an increase was not observed for areas RL and 7b (i.e., Fig. 2*C*). The mean number of active voxels for the bilateral stimulus condition was almost twice the number active in the unilateral stimulus condition (461 ± 25 vs. 731 ± 45, respectively, mean ± SD; $P < 0.05$; Fig. 3). There was no significant difference for uni- versus bilateral stimulation in the number of active voxels for RL (37.9 ± 29.8 vs. 41.0 ± 48.2) or 7b (23.1 ± 41.7 vs. 20.7 ± 44.9; Fig. 3). However, the sample size was quite small (Table 1), and individual difference, or between subject variance, was large.

A thorough examination of ipsilateral activation was not made because half of the subjects were scanned with a surface coil, which does not allow for clear images of the entire brain. Of the six subjects scanned with a whole head coil, three showed bilateral activation of S2 and PV in response to unilateral stimulation. The remaining three cases showed only contralateral activation.

TABLE 2. *Mean location of the centroid of activation in Talairach coordinate space*

Cortical Field	Talairach Coordinates		
	ML (*x*)	AP (*y*)	SI (*z*)
RL	57.0 ± 7.6	−15.6 ± 9.3	−16.0 ± 4.9
S2/PV	55.4 ± 4.3	−20.9 ± 6.6	−12.0 ± 5.9
7b	46.0 ± 4.2	−20.5 ± 14.0	−12.6 ± 1.5

In the anterior-posterior plane, RL is ~0.5 cm rostral to S2/PV and 0.4 cm inferior. The location of 7b was highly variable across subjects, especially in the anterior posterior plane, and only 5 subjects showed significant activation in 7b. Values are means ± SD.

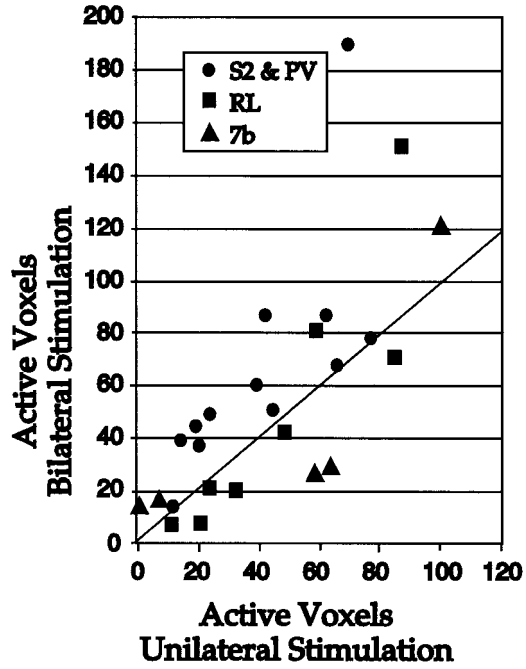

FIG. 3. A graph of individual subjects' functional magnetic resonance imaging (fMRI) data. Number of active voxels in somatosensory fields of the Sylvian fissure for uni- vs. bilateral stimulation are shown. The line through the origin indicates the location where the values for unilateral and bilateral stimulation are equal. Note that the values for S2 and PV are above this line, indicating that the number of activated voxels was greater for bilateral stimulation ($P < 0.05$). The number of subjects for the RL ($n = 7$) and 7b ($n = 2$ for unilateral and 5 for bilateral stimulation) comparisons are small and the inter-subject differences were quite large.

MEG

The MEG response to tactile stimulation had several components (Fig. 4). First, for both uni- and bilateral stimulation a large, early peak at 40 ms was localized to the postcentral gyrus in all subjects (Fig. 5*A*). This peak has been well described previously and is probably due to the activity of neurons in areas 3b and 1 (Hari et al. 1993). Because there was no difference in latency or 95% confidence volume for uni- versus bilateral stimulation, the data for these variables from the two conditions are reported together. The mean latency of the S1 peak was 42.8 ± 10.2 ms. The magnetic sources were well localized with a mean 95% confidence volume of 0.19 ± 0.18 cm^3 and a mean correlation of 0.98 ± 0.01.

A second component was a middle peak, occurring between 80 and 160 ms (mean = 87.8 ± 13.7 ms), localized to the upper bank of the Sylvian fissure for both stimulus conditions in all subjects (Figs. 4 and 5*B*). This peak is typically considered to arise from "S2" (Elbert et al. 1995; Hari et al. 1984, 1993), although distinctions between the various cortical fields residing in this region have not been made using MEG. The variance in our data was well accounted for using a single dipole (mean correlation = 0.98 ± 0.01). Thus we detected a single source at the initial S2 peak. This peak was well localized, with a mean 95% confidence volume of 0.1 ± 0.1 cm^3. Further, since our fMRI results indicate that S2/PV are consistently active to tactile stimulation while RL and 7b are not,

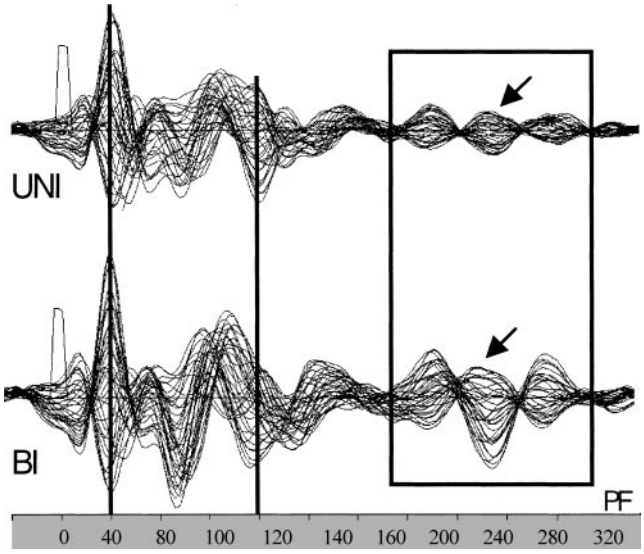

FIG. 4. Graph of magnetoencephalography (MEG) data shows magnetic field strength over time from all 37 sensors drawn with a common baseline. *Top*: activation in response to unilateral stimulation. *Bottom*: the response to bilateral stimulation. The vertical lines indicate the S1 (40 ms) and initial S2/PV (160 ms) dipole peaks. The box indicates the late response in S2/PV. The field strength of the second peak (arrow) is larger for the bilateral stimulus condition. Data from this peak were used for analysis.

the location of this second peak of activation in the Sylvian fissure is likely to be in S2 and PV. The initial S2/PV peak was located inferior to the S1 peak by an average of 1.5 ± 1.1 cm. This difference was significant ($P < 0.01$). There were no significant differences in location for the anterior-posterior or medial-lateral planes. The location in the medial-lateral plane was quite variable across subjects (SD = 1.5 cm).

A third component to the MEG response was the two to three late peaks occurring between 250 and 420 ms that also localized to the upper bank of the Sylvian fissure (Figs. 4 and 5). In 2 of the 12 subjects, no late peaks were distinguished. Thus the data on the late peaks are reported for the remaining 10 subjects. Late peaks were observed under both stimulus conditions for these 10 subjects.

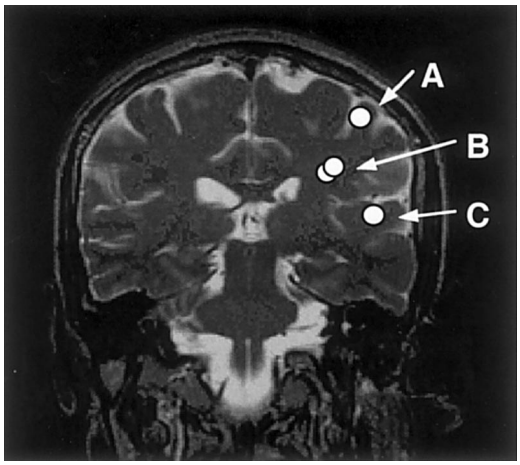

FIG. 5. A coronal magnetic resonance (MR) image with dipole localizations. The 40-ms S1 peak (*A*), initial S2/PV peak (160 ms, *B*) and the late S2 peak (*B*) are shown. For this subject, the response in auditory cortex to a 100-kHz tone is shown for comparison (*C*). The top of the head is to the top of the figure, with lateral left and right of midline.

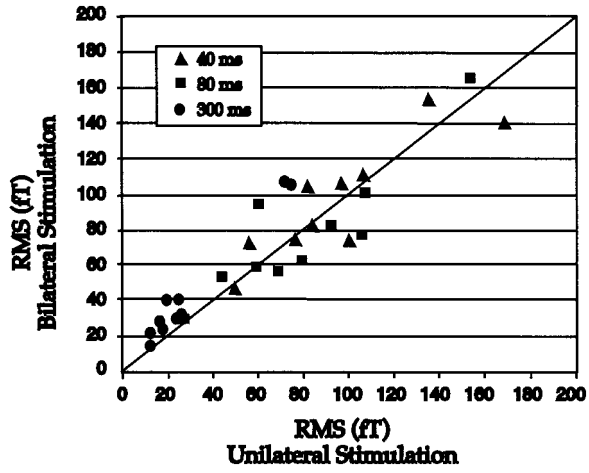

FIG. 6. A graph of individual subjects' MEG data. Evoked field strength, as measured in root mean square femoTesla [RMS(fT)], is shown for the S1, initial S2/PV, and late S2/PV peaks for uni- vs. bilateral stimulation. The line through the origin indicates the location where the values for unilateral and bilateral stimulation are equal. Note that the values for the late peak (300 ms) are above this line, indicating that evoked field strength was greater for bilateral stimulation ($P < 0.01$).

In the majority of subjects (8 of 10), there were three peaks between 250 and 420 ms (i.e., Fig. 4, box) however, in 2 of the 10 subjects, there were only two late peaks (not shown). The most robust of these responses was the second peak, which showed a dipole fit correlation of over 0.97 in all subjects for both stimulus conditions. The mean latency of the second of these peaks was 390.6 ± 27.3 ms. A single source was identified (mean correlation = 0.98 ± 0.01) with a slightly larger 95% confidence volume (mean = 1.7 ±1.3 cm^3). There were no differences in location of the late peaks from each other or from the initial S2 peak.

A comparison of magnetic field strength between stimulus conditions indicated that there was no significant difference for the early component (40 ms) localized to S1 or the middle component (80 ms) localized to S2. However, the magnetic field strength for the second peak of the late component (mean latency = 390.6 ms) was significantly larger for bilateral (mean RMS = 43.7 ± 33.6) versus unilateral (mean RMS = 30.1 ± 23.2) stimulation ($P < 0.01$; Fig. 4, arrows and Fig. 6). No comparisons were made for the first and third peaks because a robust dipole fit (correlation >0.97) was not obtained for these peaks for unilateral stimulation in several cases (4/10).

DISCUSSION

Our results demonstrate an increase in the extent of activation on the upper bank of the Sylvian fissure in humans, for bilateral versus unilateral stimulation of the hand, observed using fMRI and MEG. fMRI reveals an increased number of voxels in S2/PV for bilateral versus unilateral stimulation. Activation in areas RL and 7b was less consistent (Table 1). This inconsistency is in agreement with our previous work on this region (Disbrow et al. 1999, 2000) and may be due, in part, to the stimulus used. Neurons in RL and 7b may not respond optimally to simple somatosensory stimuli, but may prefer more complex or even multimodal stimuli.

In the temporal domain, the early responses at 40 ms (SI) and 80–160 ms (S2/PV), were not significantly different for

uni- versus bilateral stimulation, as measured using MEG. However, the magnitude of the late response (390.6 ms) was larger for bilateral versus unilateral stimulation. This late response was localized to the upper bank of the Sylvian fissure, the site of S2 and PV, where the existence of cells with bilateral receptive fields has been previously demonstrated in other primates (e.g., Robinson and Burton 1980a,b; Whitsel et al. 1969).

While previous work supports the idea that bilateral integration takes place in the somatosensory cortex on the upper bank of the Sylvian fissure, there is little agreement about the timing or the amplitude of the effect. Okajima et al. (1991) measured somatosensory evoked fields (SEFs) after electrical median nerve stimulation, comparing activation from bilateral stimulation to the sum of the SEFs from independent right and left median nerve stimulation. They saw no differences in amplitude of the early peaks (0–45 ms). However, significant interaction between the two waves occurred at the later peaks (57, 127, 223, and 364 ms). Simões and Hari (1999) also showed that input from both hands interacts in the S2 region. However, they did not present bilateral stimulation simultaneously, but staggered it by 300 ms. As in the present study Shimojo et al. (1997) observed no significant differences in the early ($<$50 ms) response for uni- versus bilateral stimulation of the tibial nerves. However, they found a decrease in the magnitude of the 80- to 90-ms peak, which localized to the upper bank of the lateral sulcus. No data on the late component were reported.

These differences between studies may be due in part to two factors, the length of the inter-stimulus interval (ISI) and the type of the stimulus. It has been shown (Hari et al. 1993, Kekoni et al. 1992) that the length of the ISI is positively correlated with the intensity of the signal localized to the S2 region (presumably our S2/PV), with no plateau in this effect for an ISI of $\leq$8 s. The studies described above were done with relatively short ISIs ($\leq$2 s) (Okajima et al. 1991; Shimojo et al. 1996; Simões and Hari 1999). We balanced practicality with previous findings (Hari et al. 1993; Kekoni et al. 1992), and used an ISI of 4 s. Discrepancies may also be due to the different types of stimuli used. In the previous work described in the preceding text, electrical stimulation of a nerve was used. In contrast, we used a tactile mechanical stimulus of calibrated indentations of the skin of the fingertips. Electrical stimulation stimulates all local receptors (or primary afferents) while tactile stimulation is more specific, which may affect the amplitude of the resulting activation. In addition, the conduction velocity for electrical stimulation is shorter than for natural tactile stimuli (Forss et al. 1994), which will affect the latency of activation.

Factors underlying differential activity for unilateral and bilateral stimulus conditions

Several inferences about the organization of somatosensory cortex can be made based on the observed fMRI and MEG signal changes in the Sylvian fissure. First, the increase in the number of active voxels and magnetic field strength may reflect an increase in the number of active neurons. In fMRI, the blood-oxygenation-level-dependent (BOLD) signal is an indirect measure of neural activity derived from changes in local oxyhemoglobin concentration associated with neural metabolism. More specifically, this technique is thought to measure changes in oxyhemoglobin related to presynaptic glucose metabolism. It has been proposed that both excitation and inhibition increase this glucose metabolism (for review, see Jueptner and Weiller 1995). Thus an increase in the number of active voxels may represent an increase in the number of excitatory and/or inhibitory postsynaptic potentials (EPSPs and IPSPs, respectively). This increase may relate to an increase in the number of active presynaptic neurons. Postsynaptically, an increase in IPSPs is more difficult to interpret because it could lead to a decrease in active neurons (inhibition) or a net increase in active neurons (disinhibition).

The evoked magnetic field measured using MEG arises from the synchronous activation of a population of neurons. It has been proposed that current flow in a large group of parallel dendrites, due to an influx or outflow of ions, results in a detectable evoked magnetic field (for review, see Gallen et al. 1995). The size of the group of dendrites would determine the strength of the evoked magnetic field. Therefore an increase in the MEG signal is consistent with an increase in the number of active presynaptic neurons (Fig. 7*D*). In fact, an increase in fMRI voxel count and MEG-evoked magnetic field have been shown in primary somatosensory cortex in response to an

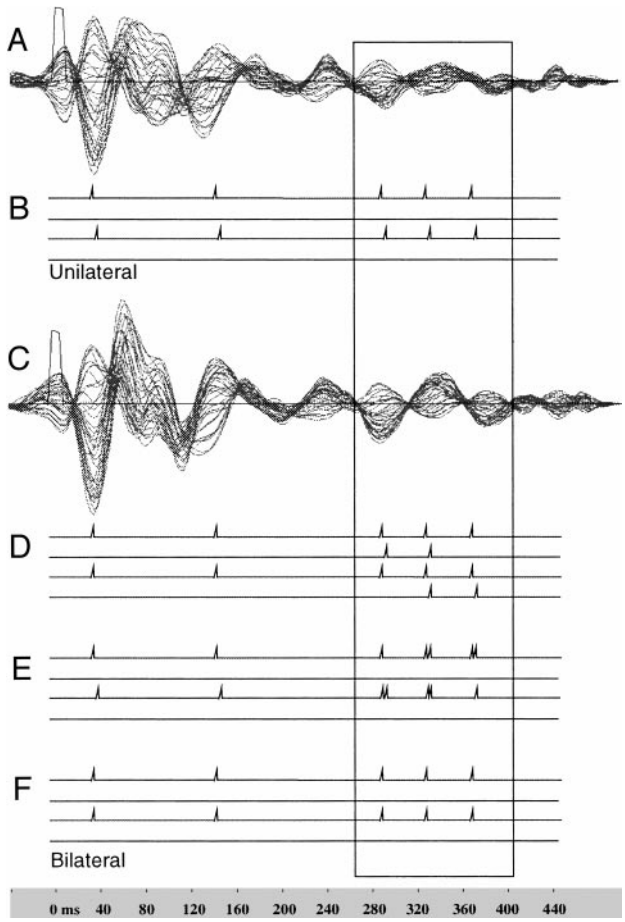

FIG. 7. Summary of factors contributing to increased magnetic field strength. The box indicates the late component. MEG data from unilateral (*A*) or bilateral (*C*) stimulation. Schematics in *B,* and *D–F* represent 4 dendrites (lines), and their activity as reflected in PSPs (deflections). For bilateral stimulation, more dendrites may be active (*D*), dendrites may have an increased rate of activity (*E*), or dendrites increase the synchrony of their response to bilateral stimulation (*F*). These changes in the activity of dendrites are a reflection of changes in neuronal activity.

increasing number of stimulated digits, and thus presumably to an increase in the number of active neurons (Roberts et al. 2000).

Several possible cortical substrates for an increase in the number of neurons responding to bilateral stimulation are suggested based on previous work in humans and other mammals. First it is possible that neurons with bilateral receptive fields require bilateral stimulation to be activated. However, although the majority of neurons in the S2 region have bilateral receptive fields, it is most likely that neurons with bilateral receptive fields would be active under both unilateral and bilateral stimulus conditions (see following text). Another possibility is that there may be neurons with entirely ipsilateral receptive fields. Results from monkey electrophysiological recording experiments suggest that a small number of neurons with exclusively ipsilateral receptive fields are present in this region (Robinson and Burton 1980b; Taoka et al. 1998). Bilateral neural responses in S2 to unilateral stimulation have been reported previously using fMRI and MEG (i.e., Disbrow et al. 2000; Hari et al. 1993), leaving open the possibility that cells with ipsilateral receptive fields exist in humans as well.

The second explanation for the increase in signal in S2/PV in response to bilateral stimulation is that there may be an increase in the firing rate of neurons under bilateral stimulus conditions (Fig. 7*E*). While neurons with bilateral receptive fields respond when a portion of the receptive field has been stimulated, in this case one hand, their rate of firing may increase when a larger portion of the receptive field is stimulated (i.e., both hands). Picard et al. (1990) have demonstrated this phenomenon in S2 of the cat. An increase in the rate of PSPs would increase the metabolic rate and yield a greater number of significantly active voxels. Although oxygen metabolism is thought to increase with increased firing rate, it is interesting to note that there was no difference in BOLD percent signal change for the uni- versus bilateral stimulus conditions. For MEG, an increase in rate of PSPs might also result in an evoked magnetic field with an increased amplitude (Fig. 7*E*).

Finally, for MEG, an increase in the synchrony of neuronal activity would result in an increase in signal intensity (Fig. 7*F*). Noncoherent dendritic current flow from a population of neurons would result in a decrease in the evoked magnetic field at any given time. Further, uncorrelated neural events could produce a situation in which nonsumming magnetic fields cancel each other out. Thus increasing temporal contiguity of PSPs would increase magnetic field strength. On the other hand, because fMRI is less temporally sensitive (20-s periods of stimulation), synchrony of neural activity is probably not a significant contributing factor to the extent of the BOLD signal.

These explanations of the number versus rate versus synchrony of neural firing are not mutually exclusive. Rather it is likely that the spatial and temporal differences observed under bilateral and unilateral stimulus conditions are due to a complex interaction between the number of active neurons and the rate at which they fire.

Hierarchical processing in the somatosensory cortex of primates

The MEG data presented here are consistent with the hypothesis that processing in the human somatosensory system is, to some extent, hierarchical. We observed a peak at 40 ms in S1, followed by a peak at 80–100 ms in S2/PV. Not until 300- to 400-ms post stimulus did we see differential activation for uni- versus bilateral stimulation. This temporal pattern of activation suggests that tactile inputs are first processed contralaterally in S1 (40 ms), then contralaterally in S2/PV (80–100 ms), and then bilaterally in S2/PV (300–400 ms).

There are several lines of evidence in nonhuman primates that indicate that sensory information is processed both in parallel and in series (e.g., Garraghty et al. 1990; Nicolelis et al. 1998; Pons et al. 1987; see Bullier and Nowak 1995; Pons et al. 1992 for review). While studies of connections indicate that all cortical areas receive thalamic inputs, and therefore have access to information from the sensory epithelium (see Jones 1985), lesion studies indicate that cortical inputs from primary areas to higher order cortical fields are necessary for driving the neurons within those fields. For instance, lesions to the primary visual area, V1, result in a loss of driven neural activity in extrastriate areas such as the second visual area, V2 (Girard and Bullier 1989), and the middle temporal visual area, MT (Kaas and Krubitzer 1992). In the somatosensory system of primates, lesions to 3a, 3b, 1, and 2 result in a loss of input to S2 from the body part representation that was lesioned (Garraghty et al. 1990; Pons et al. 1987), and a filling in of adjacent body part representations.

In humans, existing evoked potential and MEG data are also consistent with hierarchical processing. For instance, previous studies demonstrated that activity in S1 largely precedes activity in the S2 region (e.g., Elbert et al. 1995; Hari et al. 1984, 1993), and late responses to somatosensory stimulation, ~300 ms, have been reported by other laboratories (Desmedt et al. 1977; Kekoni et al. 1992; Korvenoja et al. 1995; Okajima et al. 1991). Because the differential activation for uni- versus bilateral stimulation described in the present investigation was quite late (250- to 420-ms post stimulus), these data suggest the presence of a multisynaptic circuit.

While there are direct connections between "S1" and S2/PV in monkeys (e.g., Burton et al. 1995; Friedman et al. 1986; Krubitzer and Kaas 1990), our MEG data suggest that a number of intermediate steps in processing may take place in other regions of cortex before inputs from both hands interact in S2/PV via connections from the opposite hemisphere. The anatomical substrate for extensive intrahemispheric processing has been well described in a number of studies of nonhuman primates (e.g., Jones and Powell 1969a; see Kaas and Pons 1988 for review). For instance, interconnections between anterior parietal fields 3a, 3b, 1, and 2 have been described as well as connections between anterior parietal fields and somatosensory fields in posterior parietal cortex and the lateral sulcus (the Sylvian fissure in humans). In monkeys, the representation of the hand in areas 3a and 3b is acallosal (e.g., Jones and Powell 1969b; Karol and Pandya 1971; Killackey et al. 1983; Shanks et al. 1985), and in areas 1 and 2, is almost completely acallosal (Killackey et al. 1983). Thus the site of integration of inputs between the hands must occur elsewhere in cortex. S2/PV is a viable candidate for the site of bimanual integration because patchy callosal connections have been observed throughout S2, including the representation of the hand (Karol and Pandya 1971; Krubitzer and Kaas 1990; Manzoni et al. 1984).

Taken together, the present results support the idea that there

are common features of somatosensory processing that all primates share. First, areas in the Sylvian fissure including S2 and PV are involved in processing bilateral inputs from the hands. Second, at least in part, tactile inputs are processed serially in somatosensory cortex from "S1" to S2/PV. Third, there may be extensive intrahemispheric processing of somatic inputs to the hand before information is sent to the opposite hemisphere. Finally, bilateral integration is encoded in three potential ways: increased number of neurons firing, increased rate of firing, and/or increased synchrony of firing.

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REFERENCES

BURTON H, FABRI M, AND ALLOWAY K. Cortical areas within the lateral sulcus connected to cutaneous representations in areas 3b and 1: a revised interpretation of the second somatosensory area in macaque monkeys. *J Comp Neurol* 355: 539–562, 1995.

BURTON H, MACLEOD AK, VIDEEN TO, AND RAICHLE ME. Multiple foci in parietal and frontal cortex activated by rubbing embossed grating patterns across finger pads: a positron emission tomography study in humans. *Cereb Cortex* 7: 1047–3211, 1997.

BURTON H, VIDEEN TO, AND RAICHLE ME. Tactile-vibration-activated foci in insular and parietal-opercular cortex studied with positron emission tomography: mapping the second somatosensory area in humans. *Somatosens Mot Res* 10: 297–308, 1993.

BULLIER J AND NOWAK LG. Parallel versus serial processing: new vistas on the distributed organization of the visual system. *Curr Opin Neurobiol* 5: 497–503, 1995.

CUSICK CG AND KAAS JH. *Two Hemispheres One Brain: Functions of the Corpus Callosum*. New York: Liss, 1986, p. 83–102.

CUSICK CG, WALL JT, FELLEMAN DJ, AND KAAS JH. Somatotopic organization of the lateral sulcus of owl monkeys: area 3b, S-II, and a ventral somatosensory area. *J Comp Neurol* 282: 169–190, 1989.

DESMEDT JE, ROBERTSON D, BRUNKO E, AND DEBECKER J. Somatosensory decision tasks in man: early and late components of the cerebral potential is evoked by stimulation of different fingers in random sequences. *Electroencephalogr Clin Neurophysiol* 43: 404–415, 1977.

DISBROW E, ROBERTS TPL, AND KRUBITZER L. The somatotopic organization of cortical fields in the lateral sulcus of *Homo sapiens*: evidence for SII and PV. *J Comp Neurol* 418: 1–21, 2000.

DISBROW E, ROBERTS TPL, SLUTSKY D, AND KRUBITZER L. The combined use of functional imaging and neuroanatomy to examine the second somatosensory area and surrounding cortex (Abstract). *Neuroimage* 9: S842, 1999.

DONG WK, CHUDLER EH, SUGIYAMA K, ROBERTS VJ, AND HAYASHI T. Somatosensory, multisensory and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys. *J Neurophysiol* 72: 542–564, 1994.

ELBERT T, JUNGHOFER M, SCHOLZ B, AND SCHNEIDER S. The separation of overlapping neuromagnetic sources in first and second somatosensory cortices. *Brain Topogr* 7: 275–282, 1995.

FORSS N, SALMELIN R, AND HARI R. Comparison of somatosensory evoked fields to airpuff and electric stimuli. *Electroencephalogr Clin Neurophysiol* 92: 510–517, 1994.

FRIEDMAN DP, MURRAY EA, O'NEILL JB, AND MISHKIN M. Cortical connections of the somatosensory fields of the lateral sulcus of macaques: evidence for a corticolimbic pathway for touch. *J Comp Neurol* 252: 323–347, 1986.

GALLEN CC, HIRSCHKOFF EC, AND BUCHANAN DS. Magnetoencephalography and magnetic source imaging: capabilities and limitations. *Neuroimag Clin N Am* 5: 227–249, 1995.

GARRAGHTY PE, PONS TP, AND KAAS JH. Ablations of areas 3b (SI proper) and 3a of somatosensory cortex in marmosets deactivate the second and parietal ventral somatosensory areas. *Somatosens Mot Res* 7: 125–135, 1990.

GIRARD P AND BULLIER J. Visual activity in area V2 during reversible inactivation of area 17 in the macaque monkey. *J Neurophysiol* 62: 1287–1302, 1989.

HÄMÄLIÄNEN M, HARI R, ILMONIEMI R, KNUUTILA J, AND LOUNASMAA OV. Magnetoencephalography-theory, instrumentation, and applications to noninvasive studies of the working human brain. *Rev Mod Phys* 65: 413–497, 1993.

HARI R, KARHU J, HÄMÄLÄINEN M, KNUUTILA J, SALONEN O, SAMS M, AND VILKMAN V. Functional organization of the human first and second somatosensory cortices: a neuromagnetic study. *Eur J Neurosci* 5: 724–734, 1993.

HARI R, REINIKAINEN K, KAUKORANTA E, HÄMÄLÄINEN M, ILMONIEMI R, PENTTINEN A, SALMINEN J, AND TESZNER D. Somatosensory evoked cerebral magnetic fields from SI and SII in man. *Electroencephalogr Clin Neurophysiol* 57: 254–263, 1984.

IWAMURA Y. Bilateral receptive field neurons and callosal connections in the somatosensory cortex. *Philos Trans Roy Soc Lond B Biol Sci* 355: 267–273, 1999.

IWAMURA Y, IRIKI A, AND TANAKA M. Bilateral hand representation in the postcentral somatosensory cortex. *Nature* 369: 554–556, 1994.

JONES EG. *The Thalamus*. New York: Plenum, 1985.

JONES EG AND POWELL TPS. Connexions of the somatic sensory cortex of the rhesus monkey. I. Ipsilateral cortical connections. *Brain* 92: 477–502, 1969a.

JONES EG AND POWELL TPS. Connexions of the somatic sensory cortex of the rhesus monkey. II. Contralateral cortical connections. *Brain* 92: 717–730, 1969b.

JUEPTNER M AND WEILLER C. Review: does measurement of regional cerebral blood flow reflect synaptic activity? Implications for PET and fMRI. *Neuroimage* 2: 148–156, 1995.

KAAS JH AND KRUBITZER LA. Area 17 lesions deactivate area MT in owl monkeys. *Vis Neurosci* 9: 399–407, 1992.

KAAS JH AND PONS TP. The somatosensory system of primates. *Comp Primate Biol* 4: 421–468, 1988.

KAROL EA AND PANDYA DN. The distribution of the corpus callosum in the rhesus monkey. *Brain* 94: 471–786, 1971.

KEKONI J, TIIHONEN J, AND HÄMÄLÄINEN H. Fast decrement with stimulus repetition in ERPs generated by neuronal systems involving somatosensory SI and SII cortices: electric and magnetic evoked response recordings in humans. *Int J Psychophysiol* 12: 281–288, 1992.

KILLACKEY HP, GOULD HJ, CUSICK CG, PONS TP, AND KAAS JH. The relation of corpus callosum connections to architectonic fields and body surface maps in sensorimotor cortex of New and Old World monkeys. *J Comp Neurol* 219: 384–419, 1983.

KORVENOJA A, WIKSTROM H, HUTTUNEN J, VIRTANAN J, LAINE P, ARONEN HJ, SEPPALAINEN AM, AND ILMONIEMI RJ. Activation of ipsilateral primary sensorimotor cortex by median nerve stimulation. *Neuroreport* 6: 2589–2593, 1995.

KRUBITZER L, CLAREY J, TWEEDALE R, AND CALFORD M. Interhemispheric connections of somatosensory cortex in the flying fox. *J Comp Neurol* 402: 538–559, 1998.

KRUBITZER L, CLAREY J, TWEEDALE R, ELSTON G, AND CALFORD M. A redefinition of somatosensory areas in the lateral sulcus of macaque monkeys. *J Neurosci* 15: 3821–3839, 1995.

KRUBITZER LA AND KAAS JH. The organization and connections of somatosensory cortex in marmosets. *J Neurosci* 10: 952–974, 1990.

LEDBERG A, O'SULLIVAN BT, KINOMURA S, AND ROLAND PE. Somatosensory activations of the parietal operculum of man. A PET study. *Eur J Neurosci* 7: 1934–1941, 1995.

LIN W, KUPPUSAMY K, HAACKE EM, AND BURTON H. Functional MRI in human somatosensory cortex activated by touching textured surfaces. *J Magnet Res* 6: 565–572, 1996.

MANZONI T, BARBARESI P, AND CONTI F. Callosal mechanism for the interhemispheric transfer of hand somatosensory information in the monkey. *Behav Brain Res* 11: 155–170, 1984.

NELSON RJ, SUR M, FELLEMAN DJ, AND KAAS JH. Representations of the body surface in postcentral parietal cortex of Macaca fasicularis. *J Comp Neurol* 192: 611–643, 1980.

NICOLELIS MA, GHAZANFAR AA, STAMBAUGH CR, OLIVEIRA LMO, LAUBACH M, CHAPIN JK, NELSON RJ, AND KAAS JH. Simultaneous encoding of tactile information by three primate cortical areas. *Nat Neurosci* 1: 621–630, 1998.

OKAJIMA Y, CHINO N, SAITOH E, AND KIMURA A. Recovery functions of somatosensory vertex potentials in man: interaction of evoked responses

from right and left fingers. *Electroencephalogr Clin Neurophysiol* 80: 531–535, 1991.

PICARD N, LEPORE F, PTITO M, AND GUILLEMOT JP. Bilateral interaction in the second somatosensory area (SII) of the cat and contribution of the corpus callosum. *Brain Res* 536: 97–104, 1990.

PONS TP, GARRAGHTY PE, FRIEDMAN DP, AND MISHKIN M. Physiological evidence for serial processing in somatosensory cortex. *Science* 237: 417–420, 1987.

PONS TP, GARRAGHTY PE, AND MISHKIN M. Serial and parallel processing of tactual information in somatosensory cortex of rhesus monkeys. *J Neurophysiol* 68: 518–527, 1992.

ROBERTS TPL, DISBROW EA, ROBERTS HC, AND ROWLEY HA. Quantification and reproducibility of cortical extent of activation with fMRI and MEG. *Am J Neuroradiol* 21: 1377–1387, 2000.

ROBINSON CJ AND BURTON H. Organization of somatosensory receptive fields in cortical areas 7b, retroinsula, postauditory, and granular insula of *M. fascicularis. J Comp Neurol* 192: 69–92, 1980a.

ROBINSON CJ AND BURTON H. Somatotopographic organization in the second somatosensory area of *M. fascicularis. J Comp Neurol* 192: 43–67, 1980b.

SIMÕES C AND HARI R. Relationship between responses to contra- and ipsilateral stimuli in the human second somatosensory cortex SII. *Neuroimage* 10: 408–416, 1999.

SHANKS MF, PEARSON RCA, AND POWELL TPS. The callosal connexions of the primary somatic sensory cortex in the monkey. *Brain Res Rev* 9: 43–65, 1985.

SHIMOJO M, KAKIGI R, HOSHIYAMA M, KOYAMA S, KITAMURA Y, AND WATANABE S. Intracerebral interactions caused by bilateral median nerve stimulation in man: a magnetoencephalographic study. *Neurosci Res* 24: 175–181, 1996.

STRUPP JP. Stimulate: a GUI based fMRI analysis software package. *Neuroimage* 3: S607, 1996.

TALAIRACH J AND TOURNOUX P. *Referentially Oriented Cerebral MRI Anatomy.* New York: Thieme, 1993.

TAOKA M, TODA T, IRIKI A, TANAKA M, AND IWAMURA Y. Hierarchical organization of bilateral neurons in the second somatosensory cortex of awake macaque monkeys. *Soc Neurosci Abstr* 24: 1381, 1998.

WHITSEL BL, PERTRUCELLI LM, AND WERNER G. Symmetry and connectivity in the map of the body surface in somatosensory area II of primates. *J Neurophysiol* 32: 170–183, 1969.