Somatosensory Areas Engaged During Discrimination of Steady Pressure, Spring Strength, and Kinesthesia

Anna Bodegård,¹ Stefan Geyer,² Priyantha Herath,¹ Christian Grefkes,²
Karl Zilles,^{2,3} and Per E. Roland^{1*}

¹Division of Brain Research, Department of Neuroscience, Karolinska Institute, Stockholm, Sweden

²Department of Neuroanatomy and C. & O. Vogt Brain Research Institute,
Heinrich Heine University, Düsseldorf, Germany

³Institute for Medicine, Res. Center Jülich, Jülich, Germany

Abstract: The aim of this study was to locate neuronal populations in the somatosensory areas engaged during discrimination of differences in: (1) static sustained pressure on the distal phalanx (PRESS); (2) spring strengths (SSTIFF) during active flexion of the right index finger; and (3) the change in position of a limb with contracting muscles, i.e., kinesthesia (KIN), during active flexion of the right index finger. The stimuli used were spring-loaded cylinders. The regional cerebral blood flow (rCBF) was measured with positron emission tomography (PET). The active fields were related to cytoarchitectonic areas of the somatosensory cortex (areas 3a, 3b, 1, and 2) and the primary motor cortex (areas 4a and 4p). We hypothesized that SSTIFF and KIN would activate areas 3a and 2. All three conditions, when contrasted against a rest condition, activated cytoarchitectural areas 3b, 1, and 2, and presumptive somatosensory areas in the left parietal operculum and right supramarginal gyrus in accordance with these areas receiving information from cutaneous mechanoreceptive afferents. Area 3a was only activated in SSTIFF and KIN, consistent with observations in monkeys and cats, showing that afferents from muscle receptors project to area 3a, and indicating that a similar arrangement seems to be apparent in humans. SSTIFF and KIN activated the right anterior lobe of the cerebellum, the left area 4a and left area 2 more than did PRESS, likely due to a combination of active movements and muscle receptor feed-back. *Hum. Brain Mapp.* 20:103–115, 2003. © 2003 Wiley-Liss, Inc.

Key words: PET; cytoarchitectonic mapping; human; cerebral cortex; muscle receptors; mechanoreceptors; area 3a; area 3b; area 1; area 2

INTRODUCTION

In 1959, Powell and Mountcastle [1959a] described four areas in the postcentral gyrus of the rhesus monkey. The

areas differed in their cytoarchitecture and in their response to input from skin, mechanoreceptors, and joints. The areas are known as areas 3a, 3b, 1, and 2 of the somatosensory cortex. Tactile information from skin mechanoreceptors, both slowly and rapidly adapting, is processed by areas 3b, 1, and 2 [Dykes et al., 1980; Jones and Friedman, 1982; Merzenich et al., 1978; Phillips et al., 1988; Werner and Whitsel, 1968; Whitsel et al., 1971]. Area 2 has neurons that, in addition to processing input from mechanoreceptors, respond to joint and muscle manipulation [Iwamura et al., 1983; Mountcastle and Powell, 1959a]. Area 3a neurons are driven by afferents from muscle receptors [Friedman and Jones, 1981; Jones and Porter, 1980; Phillips et al., 1971].

The ability to estimate and discriminate differences in a steady pressure exerted on the glabrous skin in primates is mediated by slowly adapting mechanoreceptors [Johansson and Vallbo, 1979; Vallbo and Hagbarth, 1968]. The afferents from slowly adapting mechanoreceptors in the glabrous skin show a sustained discharge during constant skin inden-

Contract grant sponsor: Medical Research Council of Sweden; Contract grant number: K2002-33X 09456-12B; Contract grant sponsor: Deutsche Forschungsgemeinschaft; Contract grant sponsor: National Institute of Mental Health; Contract grant sponsor: National Institute of Neurological Disorders and Stroke; Contract grant sponsor: National Institute on Drug Abuse; Contract grant sponsor: National Cancer Institute.

*Correspondence to: Per Roland, Karolinska Institute, Department of Neuroscience, Human Brain Research, Retzius väg 8, S-171 77 Stockholm, Sweden. E-mail: per.roland@neuro.ki.se

Received for publication 4 June 2002; Accepted 24 April 2003

DOI 10.1002/hbm.10125

tation and increase their discharge rate monotonically during increased pressure of the skin indentation [Knibestöl and Vallbo, 1970]. Information from these slowly adapting receptors reaches areas 3b, 1, and 2 in the monkey [Hsaio et al., 1993; Paul et al., 1972; Ruiz et al., 1995; Sur et al., 1984; Warren et al., 1986].

Information about the state of contraction in a muscle is transmitted to the central nervous system by the muscle spindles and Golgi tendon organs. The Golgi tendon organs, located in series with skeletal muscle, are sensitive to variations in contractile force. The discharge rate has shown to increase in parallel with increasing force [Crago et al., 1982]. Hence, the Golgi tendon organs are suggested to be the main contributors that provide information of how strongly the muscles are contracted. Spring stiffness or spring strength is the force required to compress a spring a certain distance and is measured in N/m [see Roland and Ladegaard-Pedersen, 1977]. Psychophysical techniques in combination with selective blockade of skin and joint afferents have provided evidence that humans can discriminate spring stiffness dependent on receptors in tendons or muscles [Roland and Ladegaard-Pedersen, 1977; Rymer and D'Almeida, 1980]. It has been debated whether or not Golgi tendon organ signals reach primary somatosensory cortex (S1) [McCloskey et al., 1983]. Electrophysiological observations of neurons in S1 of the cat, however, showed that Golgi tendon organ signals reach area 3a [McIntyre et al., 1984]. The above findings indicate that the Golgi tendon organ might play a role in providing information of differences in the state of contraction in muscles and that this information is available to somatosensory cortices, area 3a.

The muscle spindles detect changes in muscle length [Edin and Vallbo, 1988] and are generally thought to provide information of change in the position of a limb with contracting muscles (kinesthesia) [Goodwin et al., 1972; Matthews, 1977]. In monkeys, the afferents conveying information from the muscle spindles reaches areas 3a and 2 [Hore et al., 1976; Maendly et al., 1981; Phillips et al., 1971]. Naito et al. [1999] have shown that kinesthetic illusions, elicited by tendon vibration of motionless limbs in humans, are associated with activations of cortical motor areas such as area 4a, the cingulate motor areas (CMA), supplementary motor area (SMA), and premotor cortex (PM). These findings suggest that areas 3a and 2 might not be the only cortical targets for kinesthetic signals.

Based on these findings, we used spring-loaded cylinders to create sensations of sustained pressure, muscular tension, and kinesthesia in eight volunteers. We expected that all three conditions would activate areas 3b, 1, and 2 [Dykes et al., 1980; Jones and Friedman, 1982; Merzenich et al., 1978; Phillips et al., 1988; Werner and Whitsel, 1968; Whitsel et al., 1971]. The condition SSTIFF should give input from the Golgi tendon organs and in particular activate area 3a [Crago et al., 1982; McIntyre et al., 1984]. KIN would in particular recruit information from muscle spindles and consequently activate areas 3a and 2 [Hore et al., 1976; Maendly et al., 1981; Phillips et al., 1971] and the motor areas found

active during kinesthetic illusions [Naito et al., 1999]. The locations of the activated fields in the sensory and motor areas were identified with cytoarchitectonic population maps in 10 post-mortem brains [Geyer et al., 1996, 1997; Roland and Zilles, 1998].

MATERIALS AND METHODS

Eight healthy male volunteers, 23–25 years of age (mean 24 years), participated in the experiment. All volunteers gave written informed consent and the Ethics and Radiation Safety Committees of the Karolinska Institute approved the study. None of the volunteers had any previous or present history of medical or neurological diseases, and all had normal magnetic resonance (MR) scans of the brain. One was left-handed and seven were right-handed according to a Swedish version of the Oldfield [1971] questionnaire.

The stimuli used were 15 screw springs encapsulated by two cylinders (Fig. 1) and supplied with a mm scale [Roland and Ladegaard-Pedersen, 1977]. The different spring strengths and compression lengths used were determined according to prior psychophysical experiments on seven other normal healthy volunteers, such that the probability of correct discrimination would be approximately 0.80.

One condition was rest. The three other conditions were discrimination of differences in pressure (PRESS), spring strengths (SSTIFF), and in the extent of movement, i.e., kinesthesia (KIN). All four conditions were repeated three times. The volunteers had their eyes closed and ears plugged during all conditions. The volunteers did not see the stimuli before or during scanning. The stimuli were in all three conditions discriminated according to two-alternative forced choice (2-AFC) paradigm. During each rCBF measurement (50 sec) approximately seven complete cylinder pairs were discriminated in each condition.

For the PRESS discrimination task the volunteers' hand rested in a relaxed position on a soft bedding on the dorsal surface of the hand. The volunteers extended their index finger during the stimulation procedure. The experimenter pressed a spring-loaded cylinder twice onto the volar surface of the distal phalanx of the volunteers' right index finger (Fig. 1A). The maximal compression length, $s_{\max}$, of the cylinder was 10 mm. The experimenter compressed the cylinder until $s_{\max}$ was reached after ~ 1.5 sec. The cylinder was compressed slowly to ensure that the volunteers could not discriminate during the compression phase. The cylinder was gently held in the position of $s_{\max}$ for ~ 1.3 sec and care was taken not to apply any extra pressure. The cylinder was removed and the next stimulation started. The volunteers were asked to judge and verbally respond "one" or "two" depending on whether the first or second stimulus produced the strongest sustained pressure.

In SSTIFF, the second task, the volunteers' hand rested in a relaxed position on a soft bedding (the palm facing down) on their wrist, hypothenar and tips of digits 1, 3, 4, and 5. The cylinder was placed under the volar surface of the distal phalanx of the right index finger. The volunteers compressed the spring-loaded cylinder twice for a total of ~ 3.0

sec by flexing the index finger (Fig. 1B). The first cylinder was removed and after ~0.5 sec the next spring-loaded cylinder was put under the distal phalanx of the right index finger and compressed. The volunteers were asked to judge and respond verbally "one" or "two" depending on whether the first or the second cylinder had the strongest spring strength. The spring strengths used were (in Newton cm^{-1}): 0.98, 1.18, 1.47, 3.43, 3.92, 4.41, 5.88, 6.86, 7.84, 10.79, and 12.75. The extent of movement and the force used to compress the spring-loaded cylinders was balanced between the KIN and STIFF conditions such that the mean force and mean extent was equal during the first min of the scanning.

The stimulus used in the condition KIN were also spring-loaded cylinders but with an insertion cylinder of known height placed between the bottom cylinder and the upper cylinder (Fig. 1C) [Roland and Ladegaard-Pedersen, 1977].

Figure 1.

The insertion cylinder reduced the extent of movement, $s_{\max}$. The spring strengths were chosen such that maximal compression gave identical pressure force on the distal phalanx of the index finger within each discrimination pair. The volunteers hand rested in a relaxed position on a soft bedding (the palm facing down) on their wrist, hypothenar and tips of digits 1, 3, 4, and 5. The cylinder was placed under the volar surface of the distal phalanx of the right index finger. The volunteers compressed the cylinder twice for a total of ~3.0 sec by flexing the index finger. Two cylinders with different $s_{\max}$ were selected and the presentation was randomized. The volunteers had to decide and respond verbally "one" or "two" depending on which of the two cylinders could be compressed more, thus $s_{\max}$ was the entity to be discriminated. The different $s_{\max}$ of the cylinder were (in mm): 25.0, 22.0, 21.7, 18.6, 15.4, 14.0, 13.2, 11.2, 10.2, 8.5, 5.0, and 4.5.

A rest condition was also included in which the volunteers were instructed to relax, not move or think about anything in particular. The hand was in the rest condition in an anatomical resting position.

The discrimination limits and performance were calculated according to the following formula [Roland and Mortensen 1987]; $PC = \frac{1}{2} (cij/aij + cji/aji)$. PC is percent correct and is dependent on: cij, number of correct answers when the strongest pressure, spring strength or longest $s_{\max}$ were presented first; aij, number of times when the strongest pressure, spring strength or longest $s_{\max}$ were presented first; cji, number of correct answers when the lightest pressure, spring strength or shortest $s_{\max}$ were presented first; and aji, number of times when the lightest pressure, spring strength or shortest $s_{\max}$ were presented first.

We recorded the electromyogram (EMG) from the right flexor digitorum and extensor digitorum muscles, during all scans. Two electrodes were placed on the skin over the belly of the flexor and two over the belly of the extensor muscle.

Illustration of the spring-loaded cylinders used as stimuli during the three different conditions; PRESS, SSTIFF and KIN. **A:** PRESS did not involve any movement. The experimenter pressed the spring-loaded cylinder against the tip of the volunteer's right index finger and a sustained skin indentation was produced. The sustained pressure was the entity to be discriminated. **B:** SSTIFF, an active task in which the volunteer compressed the cylinder, placed under the volar surface of his right index finger, by flexing his index finger. Differences in spring strengths were the entity to be discriminated, here illustrated by a thin arrow (moderate spring strength) for the first cylinder and a fat arrow (stronger spring strength) for the second cylinder under the two alternative forced choice procedure. **C:** KIN, an active task in which the volunteer compressed the cylinder, placed under the volar surface of his right index finger, by flexing his index finger. The entity to be discriminated was differences in maximal compression, $s_{\max}$ as illustrated by the long and the short arrow. Differences in $s_{\max}$ were regulated with insertion cylinders (ic) of different sizes.

The gain of the amplifier was 2,000, and the high-cut filter was set to 20 kHz.

The skin surface stimulated during the three tasks was determined by dipping the cylinder in stamp ink and making an imprint on the skin surface of the right index finger in contact with the cylinder. The pressure exerted on the stimulated skin area was balanced so that the maximal applied spring strengths (N/cm) were practically the same, averaged over each 50-sec scan for all three conditions. The total pressure exerted on the skin area (N/cm²) integrated over time was the same in SSTIFF and KIN, but approximately 14% higher in the condition PRESS.

PET Scanning and Data Analysis

Each volunteer was wearing a personally fitted stereotactic head fixation helmet during the MR and PET scans. The 3-D MRI anatomical images were obtained as a spoiled gradient acquisition in steady state (SPGR) sequence with a General Electric Signa 1.5 T scanner. The radioactivity in the brain was measured with an ECAT-EXACT HR PET camera in 3-D mode. A catheter was inserted into the left brachial vein for injection of the tracer. Approximately 14 mCi ¹⁵O-butanol was given as a bolus injection before each scan. The emission data were corrected for attenuation through a transmission scan. The task began 10 sec before the radio-tracer was injected and continued for 100 sec. Each volunteer had a cannula inserted under local anesthesia into the left radial artery from where the radioactive tracer concentration was measured every second during scanning. The rCBF was then calculated by an autoradiographic procedure [Meyer, 1989]. The data were integrated over 50 sec, starting at the time the tracer reached the brain. The images were reconstructed with a 4-mm Hanning filter and further filtered with a 5 mm isotropic 3-D Gaussian filter. Each volunteer's rCBF images were spatially normalized using the algorithm of Woods et al. [1992]. The PET data from all volunteers were pooled in the analysis.

The rCBF images were anatomically standardized into the same reference brain (the standard brain template used is a brain, derived from a group of 21 healthy male volunteers, shown to be the least deviant) of a computerized atlas system (HBA) by using each volunteer's MR scan and the full multigrid (FMG) method [Schormann and Zilles, 1998]. All data are reported in Talairach co-ordinates, as the difference between the HBA co-ordinates and the Talairach co-ordinates are negligible [Roland et al., 1994]. The statistical significance of the rCBF changes in the images was determined with a general linear model [Ledberg, 2000]. Five-thousand Monte Carlo simulations were used for the estimation of the probability of false positive clusters of activation [Ledberg, 2000]. The simulations gave the result that clusters larger than 142 voxels (1,136 mm³) were significant, omnibus $P < 0.05$, at a t -value of 2.64.

The activations in the sensorimotor cortex were examined for their localization within cytoarchitectonic areas 44, 45, 4a, 4p, 3a, 3b, 1, and 2 [Amunts et al., 1999; Geyer et al., 1996, 1999; Schleicher et al., 1999]. The areas were mapped with

cytoarchitectonic techniques in ten post-mortem brains. The borders of each cytoarchitectonic area were determined on the basis of statistically significant differences in the laminar densities of neuronal cell bodies [Schleicher et al., 1999]. After correction of the sections for deformations due to histological processing, the 3-D reconstructed histological volumes of the individual brains and the volume representations of the cytoarchitectonic areas were warped to the same reference brain as were the PET images by using the FMG method of Schormann and Zilles [1998]. A population map was generated for each area by superimposing corresponding areas from different brains in the 3-D space of the reference brain [Roland and Zilles, 1998]. The population maps describe, for each voxel, how many brains have a representation of one particular cytoarchitectonic area. Inter-individual variations in the extent and localization of each cytoarchitectonic area led to voxels representing more than one area. In these cases, the voxel was allocated to the cytoarchitectural area to which most of the brains represented in the voxel belonged. In the case that a cytoarchitectural area did not abut another area on one side (as area 2) a 30% threshold was used to delimit the unabridged part (i.e., 30% of all brains had area 2 represented at this border). The result was a probability map of cytoarchitectural areas (Fig. 2).

The issue of whether or not a particular cytoarchitectonic area was activated was addressed by using the voxels belonging to each cytoarchitectonic area as a volume of interest (VOI). The mean rCBF in these VOIs was calculated in all images. A linear model with volunteers (8) and conditions (4) as factors and global CBF as covariate was fitted to these data. The mean rCBF in the VOIs in each discrimination condition was then contrasted against the mean rCBF in the same VOIs in the rest and other discrimination conditions. In addition, intersection volumes (in mm³) were calculated between the VOI of each cytoarchitectonic area and significant clusters. The criterion, however, for a cytoarchitectonic area to be called "activated" was set to obtain a t -value > 1.99 (corresponding to $P < 0.05$, $df = 75$) from the VOI analysis.

RESULTS

Psychophysics

PRESS

Stronger sustained pressures (N/cm²), applied to the distal phalanx of the right index finger, required larger differences in spring strengths to be discriminated compared to light pressures as illustrated in Figure 3A. During PET, 78% (SD ± 6.9) of the volunteers' responses were correct. This condition was not associated with any EMG activity. The skin area in contact with the cylinder was 2.7 cm² (SD ± 0.4)

SSTIFF

The difference required in N/cm to discriminate between springs with different strengths is shown in Figure 3B. Dur-

Figure 2.

Illustration of the congruence between the boundaries of the cytoarchitectural areas when mapped on the averaged MR image and the anatomy of the pre- and post-central gyri. The location of area 3a (brown boundary), area 3b (green boundary), area 1 (blue boundary) and area 2 (red boundary) in horizontal ($z = 37$) and sagittal ($x = -40$) section. The location of area 4a (yellow boundary) and area 4p (white boundary) in horizontal ($z = 38$) and sagittal ($x = -46$) section.

ing PET, 82% ($SD \pm 6.2$) of the volunteers responses were correct. EMG activity was observed during the compression phase only. The skin area in contact with the cylinder was 2.5 cm^2 ($SD \pm 0.6$).

KIN

The required discrimination limit in mm to discriminate between $s_{\max}$ with different length is shown in Figure 3C. During PET, 74% ($SD \pm 7.5$) of the volunteers' responses were correct. EMG activity was observed during the compression phase only. The skin area in contact with the cylinder was 2.8 cm^2 ($SD \pm 0.4$). One could argue that the discrimination of kinesthesia could be based solely on differences in spring strengths because cylinders with a long $s_{\max}$ were associated with a spring with less strength than cylinders with a short $s_{\max}$. If one examined the differences in spring strengths that were used in 30 % of the KIN discrimination pairs, however, the differences in spring strength were too small to be discriminated above chance level in the SSTIFF condition. Thus subjects could still have used spring strength as the sensory cue in the remaining 70% of the KIN discriminations, as these trials had spring strength differences that could be discriminated in the SSTIFF condition. If this was so, their percentage of correct in these 70% of the trails should be significantly better than in the 30% trials. When the performance in the 30% KIN trials was compared to the other 70%, however, the percentage of correct responses was 76% compared to 73%. We would

therefore argue that the volunteers, as instructed, paid attention to differences in $s_{\max}$ and not spring strengths. Further, it is unlikely that they would have changed discrimination strategy.

Changes in rCBF

The condition PRESS contrasted to rest produced a cluster, $7,912 \text{ mm}^3$, located in the left sensorimotor cortex (Fig. 4). The cluster overlapped with areas 3b, 1, and 2, and somewhat with area 4a. The remaining of the sensorimotor cluster extended into the dorsal premotor cortex (PMD). The parietal operculum (PO) in the left hemisphere was activated in both medial (the part of the PO lying medial to $x = \pm 45$) and lateral parts (the part of PO lying lateral to $x = \pm 45$). The left posterior part of the insula was also significantly activated (Fig. 4, Table I). The only activation in the right hemisphere was located to the supramarginal gyrus. The VOI analysis showed statistically significant increases in left hemisphere areas 3b, 1, 2, and 4a (Table II).

SSTIFF contrasted to rest produced a large cluster, $29,840 \text{ mm}^3$, located in the left sensorimotor region (Fig. 4) overlapping areas 3b, 1, and 2, and M1 (areas 4a and 4p). The centers of gravity in the cytoarchitectural areas were located 10 mm, 6.4 mm, and 2.6 mm more superior and medial compared to the locations of the activations in area 3b, 1, and 2 in the PRESS-rest contrast (Tables I, III). This sensorimotor cluster extended into the PMD, the CMA, the SMA, and into the cortex lining the superior parts of the intraparietal sul-

Figure 3.

Discrimination thresholds for pressure, sense of spring stiffness and kinesthesia (80% correct responses). Psychophysical data averaged for seven volunteers. **A:** PRESS. Discrimination limits for discriminating pressure applied to the tip of the index finger. **B:** SSTIFF. Discrimination limit for discriminating spring strengths, by flexing the index finger. **C:** KIN. Discrimination limit for discriminating differences in maximal compression, $s_{\max}$, by flexing the right index finger.

cus. Laterally, the cluster extended to the PO. Significant activations in the right hemisphere were localized in the supramarginal gyrus, cytoarchitectonic areas 44 and 45, and lateral parts of the PO (Fig. 4). The anterior lobe of the cerebellum was activated bilaterally, the posterior lobe was

activated in the left hemisphere (Fig. 4, Table III). The VOI analysis showed statistically significant increases in rCBF in left areas 3a, 3b, 1, 4a (Table II) and bilaterally in area 2 (area 2 right $t = 2.85$; $P < 0.01$).

The condition KIN contrasted to rest produced a large cluster, 24,480 mm³, which covered the left sensorimotor region (Fig. 4). The cluster overlapped with areas 3b, 1, 2, 4a, and 4p. The centres of gravity in the cytoarchitectural areas were located 10 mm, 5.3 mm, and 1.5 mm superior and medial in comparison to the locations of the activations in area 3b, 1, and 2 in the PRESS-rest contrast. The cluster extended into the PMD and the cortex lining the superior part of the intraparietal sulcus and extended laterally to the superior part of the insula. In addition, KIN vs. rest activated the PO, SMA, CMA, and PM bilaterally. The PO in the left hemisphere was activated in both medial and lateral parts, whereas the PO in the right hemisphere was activated in the lateral part only (Fig. 4). Additional activations in the left hemisphere were found in the ventral-lateral thalamus and posterior lobe of the cerebellum (Fig. 4). Further additional activations in the right hemisphere engaged parts of the cortex lining the superior part of the intraparietal sulcus, areas 44/45, and the anterior lobe of the cerebellum (Fig. 4, Table IV). The VOI analysis showed statistically significant increases in the rCBF in left areas 3a, 3b, 1 and bilaterally in area 2 (Table II; area 2 right $t = 2.31$; $P < 0.025$).

Significant Cortical Activations in Test vs. Test

One additional way to identify activations in SSTIFF and KIN is to contrast away the pressure factor, i.e., the pressure exerted on the skin of the volar surface of the distal phalanx of the right index finger. These contrasts (i.e., SSTIFF vs. PRESS and KIN vs. PRESS) will show activations related to the voluntary movements and the signals delivered from the muscle receptors in the flexor muscles of the finger and forearm and identify their somatotopical representation.

The contrast between SSTIFF and PRESS gave two clusters significantly more activated by SSTIFF. One cluster was located in the left sensorimotor cortex extending somewhat into the PM, overlapping with parts of areas 3b, 4a and 4p. The second cluster was found in the right cerebellum, anterior lobe (Table V). The VOI analysis showed statistically significant activations in left areas 3a, 3b, 2 (Table II).

The contrast between KIN and PRESS resulted in two clusters significantly more activated by KIN. One cluster was located in the left sensorimotor cortex, overlapping with areas 3b, 1, and 4a. The second cluster was found in right cerebellum, anterior lobe (Table VI). The VOI analysis showed statistically significant activations in left areas 3a, 3b, 2 (Table II). These clusters overlapped the clusters of the STIFF-PRESS contrast.

No significant activations were found in the contrast between SSTIFF and KIN.

There were large deactivations in the visual cortex in all three conditions when contrasted to rest. The deactivations were located in the visual areas in the occipital and parietal lobes. Deactivations during all three conditions were also

Figure 4.

The columns represent regions that were activated in the contrast between, from left to right, SSTIFF vs. rest, KIN vs. rest, and PRESS vs. rest superimposed on the standard brain. Talairach coordinates indicated. First row ($z = 47$). Strong activations in sensorimotor cortex and premotor cortex in all conditions. Bilateral activations in intraparietal cortex and CMA in SSTIFF and KIN. Second row (SSTIFF and KIN: $z = 25$, PRESS: $z = 18$). Activation in areas 44 and 45 in SSTIFF (right) and KIN (bilaterally). Bilateral activations in parietal operculum in SSTIFF and KIN, left sided activation in parietal operculum in PRESS. Third row ($z = 7$). Activation in left thalamus in KIN in addition to bilateral activation in temporal gyrus. Left sided activation in temporal gyrus is also shown in SSTIFF in addition to an activation in insula on the left side in PRESS. Bottom row ($z = -33$). Bilateral activations in cerebellum in SSTIFF and KIN.

located in the cortex lining the left superior frontal sulcus when contrasted against rest.

DISCUSSION

In this PET study we demonstrated that when volunteers discriminated sustained pressure, spring strengths and the extent of voluntary movements, significant activations in all three conditions appeared in the somatosensory areas 3b, 1,

2, in area 4a, and the PMD. Other, presumably somatosensory, areas in the medial and lateral parts of the PO and the right supramarginal gyrus were activated as well. The conditions associated with movements and judgments of signals from muscle and tendon receptors (SSTIFF and KIN) activated the contralateral (left) somatosensory areas 3a and 2 significantly more than did (PRESS). Also STIFF and KIN activated areas 4a, and 4p and the right anterior lobe of the cerebellum more than did PRESS. There were no differences

TABLE I. Significant increases of rCBF of subjects discriminating differences in pressure with their right index finger contrasted with rest

Area	mm ³	x	y	z	Z*
Left hemisphere					
Sensorimotor cortex	7910	41	-22	50	3.29
PMD					
Area 4a	260	41	-17	42	3.26
Area 3b	2720	44	-37	44	3.02
Area 1	2120	46	-29	48	3.23
Area 2	1600	43	-33	44	2.85
Posterior parts of insula, PO	1840	45	-17	42	3.40
Right hemisphere					
Supramarginal gyrus	1384	-58	-38	34	3.42

Talairach coordinates *x*, *y*, *z* signify the center of gravity of the activation.

* Z values are expressed as means.

rCBF, regional cerebral blood flow; PMD, dorsal premotor cortex; PO, parietal operculum.

between the KIN and STIFF conditions. Both activated the SMA, CMA, PMD, 4a,4p motor areas, the somatosensory areas 3a, 3b, 1, 2, IPA, and anterior part of the supramarginal gyrus, the medial and lateral PO, the left posterior lobule, and the right anterior lobule of the cerebellum.

The rest and the test conditions differed in several respects. The tests required presumably increased general attention and attention toward the somatosensory input. In addition, the volunteer needed a short-term memory to compare the sensory information in stimulus interval 1 with that of stimulus interval 2. Furthermore, the volunteer answered verbally during the tests. In principle, all observed differences in the activation of the brain when test was contrasted to rest could be due to these factors. These factors could thus explain the general activation patterns in the test vs. rest comparisons. The task-related differences in the forearm-hand sector [see Bodegård et al., 2001] of cytoarchitectural areas 3a, 3b, 1, and 2 most likely reflect differences in somatosensory attention, signals received in these areas, and

TABLE III. Significant increases of rCBF of subjects discriminating spring strengths (SSTIFF) with their right index finger contrasted with rest

Area	mm ³	x	y	z	Z*
Left hemisphere					
Sensorimotor cortex, sup. parts of IPA	29,840	30	-20	51	3.71
PMD, CMA, SMA, PO					
Area 4a	2,760	35	-23	51	4.18
Area 4p	960	34	-21	43	3.79
Area 3b	1,960	39	-29	47	3.78
Area 1	3,280	42	-32	52	3.85
Area 2	2,600	41	-35	45	3.57
Cerebellum lob anterior	1,496	9	-59	-30	3.22
Cerebellum lob posterior	1,344	34	-51	-37	3.15
Right hemisphere					
Supramarginal gyrus	2,744	-53	-37	34	3.19
PO (LPO)	1,880	-36	-51	44	3.25
Areas 44/45, PMV	1,472	-46	16	27	3.12
Superior temporal gyrus	1,488	-55	-34	6	2.98
Cerebellum lob anterior	8568	-16	-52	-25	3.40

Talairach coordinates *x*, *y*, *z* signify the center of gravity of the activation.

* Z - values are expressed as means.

CMA, cingulate motor areas; SMA, supplementary motor area; LPO, lateral parietal operculum; PMV, premotor, ventral.

their further analysis. The many differences in rCBF between conditions associated with movements (SSTIFF and KIN) and the condition not associated with movements (PRESS) may reflect the voluntary control of the movements rather than the actual discriminations of kinesthesia and spring strength.

The combination of functional imaging- and post-mortem techniques in the human brain is a novel approach. The combined use of these two techniques provides us with an observer independent possibility to localize activations in cytoarchitecturally defined areas. Some caution needs to be exercised, however, when interpreting the results. The cytoarchitectural areas are probability maps. This means that in

TABLE II. Student's t-values from the VOI analysis of the hand-finger sector (z = 34–54) of cytoarchitectural areas 3a, 3b, 1 and 2

	Area 3a	Area 3b	Area 1	Area 2	Area 4a	Area 4p
Left hemisphere						
SSTIFF-rest	2.60	5.10	3.87	7.44	6.01	3.82
Kin-rest	2.52	4.90	3.44	6.67	6.21	3.50
Press-rest	—	2.35	3.66	5.17	2.07	—
SSTIFF-press	2.49	2.78	—	2.37	3.95	2.84
Kin-press	2.40	2.60	—	2.01	4.15	2.53
Right hemisphere						
SSTIFF-rest				2.85		
Kin-rest				2.31		

VOI, volume of interest; SSTIFF, spring strength.

TABLE IV. Significant increases of rCBF of subjects discriminating kinaesthesia (KIN) with their right index finger contrasted with rest

Area	mm ³	x	y	z	Z*
Left hemisphere					
Sensorimotor cortex, PMD	24480	37	-24	49	3.76
Superior parts of IPA					
Area 4a	3050	37	-22	49	4.26
Area 4p	920	35	-20	42	3.67
Area 3b	2140	40	-28	46	3.76
Area 1	3150	43	-31	52	3.96
Area 2	2500	42	-34	45	3.40
SMA, anterior cing	6264	5	2	50	3.54
PO (L + M)	1160	46	-30	13	3.16
Thalamus	1760	9	-21	2	3.40
Cerebellum lob posterior	1736	9	-60	-32	3.13
Right hemisphere					
Superior parts of the IPA	1672	-37	-47	43	3.27
Supramarg. gyrus, LPO	5656	-55	-32	25	3.27
Areas 44/45, PMV	2336	-50	14	22	3.15
Cerebellum lob. anterior	9968	-15	-54	-27	3.47

Talairach coordinates *x*, *y*, *z* signify the center of gravity of the activation.

* Z values are expressed as means.

a statistical sense the VOIs used do not contain one area only. For example, the VOI called area 3b consists also to some extent of the neighboring areas 3a and 1. Still, the probability is larger that the voxels in the 'area 3b VOI' belongs to area 3b than to any other area. Also, the methods used to compile the data have, to some extent, introduced a variance in the localization of the central and postcentral gyri of the anatomically standardized individual brains. The mean MRI image and the cytoarchitectural population maps show the mean position of the central and postcentral gyri when averaged over all subjects' brains and transformed to the same anatomical reference brain format. The accuracy of standard anatomical transformations using the FMG

TABLE V. Significant increases of rCBF in the contrast spring strength discrimination vs. pressure discrimination

Area	mm ³	x	y	z	Z*
Left hemisphere					
Sensorimotor cortex	1176	15	-26	57	2.96
Ext. into SMA					
Area 4a	464	17	-28	58	3.03
Area 4p	192	16	-28	57	2.99
Area 3b	167	23	-31	56	2.87
Right hemisphere					
Cerebellum lob. anterior	3632	-17	-49	-25	3.22

Talairach coordinates *x*, *y*, *z* signify the centre of gravity of the activation.

* Z - values are expressed as means.

TABLE VI. Significant increases of rCBF in the contrast kinaesthesia discrimination versus pressure discrimination

Area	mm ³	x	y	z	Z*
Left hemisphere					
Sensorimotor cortex	1800	34	-23	54	
Area 4a	848	30	-21	56	
Area 3b	248	33	-27	52	
Area 1	240	34	-31	57	2.95
Right hemisphere					
Cerebellum lob. ant	2968	-14	-53	-25	3.26

Talairach coordinates *x*, *y*, *z* signify the centre of gravity of the activation.

* Z - values are expressed as means.

method is high [Crivello et al., 2002; Schormann and Zilles, 1998]. The VOIs used are large (at least 3,200 mm³ [area 3a]). The congruence between the localization of the central and postcentral gyri and the cytoarchitectural areal borders is good (Fig. 2). It is therefore unlikely that errors in the allocation to cytoarchitectural areas should have influenced the VOI results to a major degree. The interpretation of the results from the VOI analysis should be done on the basis of the above information, however, and the obtained results should be used as 'strong indications.'

Cytoarchitectonic area 3a was significantly activated in the conditions KIN and SSTIFF when contrasted against rest. Area 3a was also more strongly activated in these conditions when contrasted to PRESS (Table II). This indicates that area 3a is more activated when the voluntary movement is carried out against a spring loading as opposed to the condition of pressure discrimination in which the finger is motionless and the forearm muscles relaxed. Motion against a spring efficiently excite muscle spindles and Golgi tendon organs [Johansson and Vallbo, 1979; Roland and Ladegaard-Pedersen, 1977]. The activation of area 3a is in agreement with the observations that this area in cats and monkeys receives input from Golgi tendon organs and muscle spindles [Friedman and Jones, 1981; Grant et al., 1975; Hore et al., 1976; Landgren and Silfvenius, 1969; Maendly et al., 1981; McIntyre et al., 1984; Oscarsson and Rosén, 1963; Phillips et al., 1971]. In a functional imaging study carried out on humans, the cortex lining the fundus of the central sulcus was found active during a motor condition, whereas the same region was not found active during a passive tactile condition [Moore et al., 2000]. Our results add that area 3a indeed is active in conditions in which voluntary movements are carried out to sample signals from muscles and tendons.

Areas 3b, 1, and 2 were active in all discrimination tasks when contrasted to rest. These are findings in accordance with monkey studies, which have shown the function and significance of these areas in information processing and categorization of tactile stimulus [Dykes et al., 1980; Jones and Friedman, 1982; Merzenich et al., 1978; Phillips et al., 1988; Werner and Whitsel, 1968; Whitsel et al., 1971; Zainos

et al., 1997]. These findings give further support that the organization of the cytoarchitecturally defined areas in humans is similar to the organization within monkey S1. Interestingly, area 3b was specifically more activated when contrasting SSTIFF and KIN against PRESS. If the nerves to the cutaneous receptors are anesthetized there is a slight loss of kinesthetic sensibility [Gandevia and McCloskey, 1976; Goodwin et al., 1972; Roland and Ladegaard-Pedersen, 1977]. More specifically, slowly adapting mechanoreceptors (SAI and SAII) have been suggested to provide information about joint configurations and play a specific role in proprioception, kinesthesia and motor control [Edin, 1992; Edin and Johansson, 1995]. The integrated pressure over time exerted on the distal phalanx of the index finger was higher in the PRESS condition, as compared to the KIN and STIFF conditions, yet the 3b rCBF was somewhat higher in the KIN and STIFF conditions. This difference, however did not appear at the center of gravity for the index finger distal phalanx stimulation (Tables I, V, VI). There was no specific activation in area 3b in response to KIN when compared SSTIFF, which suggests that no selective attention to information from SA receptors occur when solving the kinesthetic task.

Area 2, which was activated in PRESS, was activated significantly stronger in SSTIFF and KIN. This finding is in accordance with Mountcastle and Powell's [1959b] observation that area 2 has a larger proportion of input from deep tissue than have areas 3b and 1. The area 2 activation could include activation due to projections from area 3a [Jones et al., 1978]. Thus the arrangement of cutaneous versus deep input to the somatosensory areas in the postcentral gyrus might be similar in higher primates. As for area 3b the activation could reflect firing of the slowly adapting skin stretch receptors located over the metacarpophalangeal joint. Interestingly, area 2 was activated ipsilaterally to the stimuli in both SSTIFF and KIN. Bilateral activations in the presumed S1 during a strictly unilateral tactile stimulation have been reported [Boecker et al., 1995; Burton et al., 1997; Hansson and Brismar, 1999; Schnitzler et al., 1995]. The only bilateral activation in the postcentral gyrus in our study, however, was located in area 2. This is in accordance with findings that showed that transcallosal connections between areas 3a, 3b, and 1 in monkeys are sparse or nearly absent for the hand region, but relatively more abundant in area 2 [Killackey et al., 1983]. Area 2 is also the only postcentral somatosensory area reported to hold neurons with bilateral receptive fields [Iwamura et al., 1994].

This study was not designed to investigate any somatotopical organization. When calculating the overlap between the significant clusters and the cytoarchitectural areas, however, we noticed that the activation of the somatosensory areas 3b, 1 and 4a during PRESS had a smaller extent and a centre of gravity located lateral and inferior compared to the activations associated with SSTIFF and KIN. The centre of gravity in PRESS – rest in cytoarchitectural areas 3b and 1 were approximately 10 and 6 mm, respectively, more lateral and inferior than those of SSTIFF – rest and KIN – rest. This

indicates that KIN and SSTIFF gave rise to activations which were extending into somatotopical representations of other parts of the body than that of the index finger. The representation of the index finger in humans in the postcentral gyrus has *x* coordinates around 37–40 and *z* coordinates of approximately 35–45 in Talairach space [Gelnar et al., 1998; Roland, 1987; Sakai et al., 1995]. The activations in areas 3b and 1 in SSTIFF and KIN are located more superior and medial than is the representation of the index finger and hand [Gelnar et al., 1998; Ibáñez et al., 1995; Roland, 1987; Sakai et al., 1995]. This activation most likely occupies the space receiving somatosensory input from the forearm [Ehrsson et al., 2000; Naito et al., 1999]. The localization of the significant clusters within area 2 did practically not differ (~2 mm). Thus, afferent information from the receptors active during SSTIFF and KIN seems to activate sectors proximal to the location of the distal phalanx of the right index finger whereas the skin receptors excited in PRESS activate the finger representation only. This might be because during the compression of the springs in KIN and SSTIFF, the finger and forearm muscles and their muscle and tendon receptors become active as shown by the EMG recordings and that subjects attend to the length and tension signals from these muscles. Alternatively that deep mechanoreceptors in the skin would be recruited by the deformation of the contracting muscles.

The contralateral area 4a was active in the PRESS condition. The volunteers, however, extended their index finger in the PRESS condition during the stimulation procedure. This is a static motor position, which recruits muscle activity in the intrinsic hand muscles to stabilize the finger. The hand was in the rest condition in an anatomical resting position. Thus, the 4a activation, in the hand/finger sector could reflect these differences in posture. That motor areas 4a/4p, in addition to the PM, SMA, and CMA, are active during stimulation of muscle spindles has recently been demonstrated [Naito et al., 1999]. In the Naito et al. [1999] study, the volunteers neither responded, nor made any verbal answers or decisions about the sensory stimuli. In the present study, we can not differentiate whether these motor area activations of left 4a and PM in PRESS – rest were due to the sensory information arriving in the motor areas, posture differences of the index finger, decision or verbal answers. The only differences in the activation pattern in the motor areas, besides area 3a, between the PRESS and the KIN and SSTIFF conditions were that the latter two conditions activated 4a/4p more in the forearm sector (Tables V, VI) than did PRESS. It might be a general observation that somatosensory information reaches motor areas under different task-related conditions. The interpretation of these motor area activations may therefore vary from test condition to test condition [Naito et al., 1999; Romo et al., 1998, 1999; Zhang et al., 1997]. In addition the ipsilateral anterior lobe of the cerebellum was activated by STIFF and KIN but not by press. This might be a general difference between active motion and passive position [Bodegård et al., 2001].

We observed consistent decreases in the rCBF in the posterior part of the parietal cortex and in the occipital cortex, regions most likely to be visual areas. We attribute this to cross-modal attentional mechanisms most likely decreasing the rCBF (and synaptic activity) in visual areas whenever volunteers focus their attention on somatosensory tasks [Bodegård et al., 2000; Drevets et al., 1995; Haxby et al., 1994; Kawashima et al., 1995].

In summary, we have demonstrated that the discrimination of pressure, spring stiffness and kinesthesia activates somatosensory areas 3b, 1, 2, the supramarginal gyrus, and the parietal operculum in humans. Furthermore our data indicates that also motor areas 4a and PM are activated during somatosensory discrimination tasks. The differences between active discrimination (against a spring load) and discrimination of pressure in which volunteers had their limbs immobile were activations in left area 3a, and in the anterior lobe of the cerebellum. When volunteers actively discriminated spring stiffness and kinesthesia, their muscle spindles and tendon organs were undoubtedly active. Because the muscles flexing the index finger are located in the finger and forearm, corresponding finger and forearm activation was seen during spring stiffness and kinesthetic discrimination in areas 3b and 1, whereas only finger representation was seen in pressure discrimination. This study also confirmed in humans the original observation in monkeys by Mountcastle and Powell [1959b] that area 3a and presumed area 2 were more activated by information from "deep receptors", most likely to be muscle spindles and tendon organs.

ACKNOWLEDGMENTS

This research was supported by the National Research Council of Sweden, the National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, National Institute on Drug Abuse, and the National Cancer Institute that jointly funded the Human Brain Project/Neuroinformatics Research. We thank H. Ehrsson for valuable comments on an earlier version on the manuscript.

REFERENCES

- Amunts K, Schleicher A, Burgel U, Mohlberg H, Uylings HB, Zilles K (1999): Broca's region revisited: cytoarchitecture and intersubject variability. *J Comp Neurol* 412:319–341.
- Bodegård A, Geyer S, Naito E, Zilles K, Roland PE (2000): Somatosensory areas in man activated by moving stimuli. Cytoarchitectonic mapping and PET. *NeuroReport* 11:187–191.
- Bodegård A, Geyer S, Grefkes C, Zilles K, Roland PE (2001): Hierarchical processing of tactile shape in the human brain. *Neuron* 31:317–328.
- Boecker H, Khorram-Sefat D, Kleinschmidt A, Merboldt K-D, Hancic W, Requardt M, Frahm J (1995): High-resolution functional magnetic resonance imaging of cortical activation during tactile exploration. *Hum Brain Mapp* 3:236–244.
- Burton H, MacLeod AM, Videen TO, Raichle ME (1997): 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* 7:3–17.
- Crago PE, Houk JC, Rymer WZ (1982): Sampling of total muscle force by tendon organs. *J Neurophysiol* 47:1069–1083.
- Crivello F, Schormann T, Roland PE, Zilles K, Mazoyer BM (2002): A comparison of spatial normalization procedures and their impact on functional maps. *Hum Brain Mapp* 16:228–250.
- Drevets WC, Burton H, Videen TO, Snyder AZ, Simpson JR, Raichle ME (1995): Blood flow changes in human somatosensory cortex during anticipated stimulation. *Nature* 373:249–252.
- Dykes RW, Rasmusson DD, Hoeltzel PB (1980): Organization of primary somatosensory cortex in the cat. *J Neurophysiol* 43:1527–1546.
- Edin BB, Vallbo AB (1988): Stretch sensitization of human muscle spindles. *J Physiol* 400:101–111.
- Edin BB (1992): Quantitative analysis of static strain sensitivity in human mechanoreceptors from hairy skin. *J Neurophysiol* 67:1105–1113.
- Edin BB, Johansson N (1995): Skin strain patterns provide kinesthetic information to the human central nervous system. *J Physiol* 15:243–251.
- Ehrsson HH, Naito E, Geyer S, Amunts K, Zilles K, Forssberg H, Roland PE (2000): Simultaneous movements of upper and lower limbs are coordinated by motor representations that are shared by both limbs: a PET study. *Eur J Neurosci* 12:3385–3398.
- Friedman DP, Jones EG (1981): Thalamic input to areas 3a and 2 in monkeys. *J Neurophysiol* 45:59–85.
- Gandevia SC, McCloskey DI (1976): Joint sense, muscle sense, and their combination as position sense, measured at the distal interphalangeal joint of the middle finger. *J Physiol* 260:387–407.
- Gelnar PA, Krauss BR, Szevenyi NM, Apkarian AV (1998): Fingertip representation in the human somatosensory cortex: an fMRI study. *Neuroimage* 7:261–283.
- Geyer S, Ledberg A, Schleicher A, Kinomura S, Schormann T, Larson J, Simon U, Zilles K, Roland PE (1996): Two different areas within the primary motor cortex of man. *Nature* 382:805–807.
- Geyer S, Schleicher A, Zilles K (1997): The somatosensory cortex of human: cytoarchitecture and regional distributions of receptor-binding sites. *Neuroimage* 6:27–45.
- Geyer S, Schleicher A, Zilles K (1999): Areas 3a, 3b, and 1 of human primary somatosensory cortex. *NeuroImage* 10:63–83.
- Goodwin GM, McCloskey DI, Matthews PB (1972): The contribution of muscle afferents to kinesthesia shown by vibration induced illusions of movement and by the effects of paralyzing joint afferents. *Brain* 95:705–748.
- Grant G, Landgren S, Silfvenius H (1975): Columnar distribution of U-fibers from the postcruciate cerebral projection area of the cat's group I muscle afferents. *Exp Brain Res* 24:57–74.
- Hansson T, Brismar T (1999): Tactile stimulation of the hand causes bilateral cortical activation: a functional magnetic resonance study in humans. *Neurosci Lett* 13:29–32.
- Haxby JV, Horwitz B, Ungerleider LG, Maisog JM, Pietrini P, Grady CL (1994): The functional organization of human extrastriate cortex: a PET-rCBF study of selective attention to faces and locations. *J Neurosci* 14:6336–6353.
- Hore J, Preston JB, Cheney PD (1976): Responses of cortical neurons (areas 3a and 4) to ramp stretch of hindlimb muscles in the baboon. *J Neurophysiol* 39:484–500.
- Hsiao SS, Johnson KO, Twombly IA (1993): Roughness coding in the somatosensory system. *Acta Psychol (Amst)* 84:53–67.
- Ibáñez V, Deiber MP, Sadato N, Toro C, Grissom J, Woods RP, Maziotta JC, Hallet M (1995): Effects of stimulus rate on regional cerebral blood flow after median nerve stimulation. *Brain* 118:1339–1351.

- Iwamura Y, Tanaka M, Sakamoto M, Hikosaka O (1983): Functional subdivisions representing different finger regions in area 3 of the first somatosensory cortex of the conscious monkey. *Exp Brain Res* 51:315–326.
- Iwamura Y, Iriki A, Tanaka M (1994): Bilateral hand representation in the postcentral somatosensory cortex. *Nature* 16:554–556.
- Johansson RS, Vallbo AB (1979): Tactile sensibility in the human hand: relative and absolute densities of four types of mechanoreceptive units in the glabrous skin area. *J Physiol (London)* 286:293–300.
- Jones EG, Coulter JD, Hendry SH (1978): Intracortical connectivity of architectonic fields in the somatic sensory, motor and parietal cortex of monkeys. *J Comp Neurol* 181:291–347.
- Jones EG, Porter R (1980): What is area 3a? *Brain Res Rev* 2:1–43.
- Jones EG, Friedman DP (1982): Projection pattern of functional components of thalamic ventrobasal complex on monkey somatosensory cortex. *J Neurophysiol* 48:521–544.
- Kawashima R, Roland PE, O'Sullivan BT (1994): Activity in the human primary motor cortex related to ipsilateral hand movements. *Brain Res* 14:251–256.
- Kawashima R, O'Sullivan BT, Roland PE (1995): Positron-emission tomography studies of cross-modality inhibition in selective attentional tasks: closing the “mind’s eye”. *Proc Natl Acad Sci USA* 92:5969–5972.
- Killackey HP, Gould HJ 3-D, Cusick CG, Pons TP, Kaas JH (1983): 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* 1:384–419.
- Knibestöl M, Vallbo AB (1970): Single unit analysis of mechanoreceptor activity from the human glabrous skin. *Acta Physiol Scand* 80:178–195.
- Landgren S, Silfvenius H (1969): Projection to cerebral cortex of group I muscle afferents from the cat’s hindlimb. *J Physiol* 200:353–372.
- Ledberg A (2000): Robust estimation of the probabilities of 3-D clusters in functional brain images: application to PET data. *Hum Brain Mapp* 9:143–155.
- Maendly R, Rüllegg DG, Wiesendanger M, Wiesendanger R, Lagowska J, Hess B (1981): Thalamic relay for group I muscle afferents of forelimb nerves in monkey. *J Neurophysiol* 46:901–917.
- Matthews PB (1977): Muscle afferents and kinesthesia. *Br Med Bull* 33:137–142.
- Merzenich MM, Kaas JH, Sur M, Lin CS (1978): Double representation of the body surface within cytoarchitectonic areas 3b and 1 in “SI” in the owl monkey (*Aotus trivirgatus*). *J Comp Neurol* 181:141–173.
- Meyer E (1989): Simultaneous correction for tracer arrival delay and dispersion in CBF measurements by the $H_2^{15}O$ autoradiographic method and dynamic PET. *J Nucl Med* 30:1069–1078.
- McCloskey DJ, Cross MJ, Honner R, Potter EK (1983): Sensory effects of pulling or vibrating exposed tendons in man. *Brain* 106:21–37.
- McIntyre AK, Proske U, Rawson JA (1984): Cortical projection of information from tendon organs in the cat. *J Physiol (Lond)* 354:395–406.
- Moore CI, Stern CE, Corkin S, Fischl B, Gray AC, Rosen BR, Dale AM (2000): Segregation of somatosensory activation in the human Rolandic cortex using fMRI. *J Neurophysiol* 84:558–569.
- Mountcastle VB, Powell TPS (1959a): Central nervous mechanisms subserving position sense and kinesthesia. *Bull Johns Hopkins Hosp* 105:173–200.
- Mountcastle VB, Powell TPS (1959b): Neural mechanisms subserving cutaneous sensibility, with special reference to the role of afferent inhibition in sensory perception and discrimination. *Bull Johns Hopkins Hosp* 105:201–232.
- Naito E, Ehrsson HH, Geyer S, Zilles K, Roland PE (1999): Illusory arm movements activate cortical motor areas: a PET study. *J Neurosci* 19:6134–6144.
- Oldfield RC (1971): The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9:97–113.
- Oscarsson O, Rosén I (1963): Projection to cerebral cortex of large muscle-spindle afferents in forelimb nerves of the cat. *J Physiol (Lond)* 169:924–945.
- Paul RL, Merzenich M, Goodman H (1972): Representation of slowly and rapidly adapting cutaneous mechanoreceptors of the hand in Brodmann’s areas 3 and 1 of *Macaca mulatta*. *Brain Res* 36:229–249.
- Phillips CG, Powell TPS, Wiesendanger M (1971): Projection from low threshold muscle afferent of hand and forearm to area 3a of baboon’s cortex. *J Physiol Lond* 217:419–446.
- Phillips JR, Johnson KO, Hsiao SS (1988): Spatial pattern representation and transformation in monkey somatosensory cortex. *Proc Natl Acad Sci U S A* 85:1317–1321.
- Powell TPS, Mountcastle VB (1959): The cytoarchitecture of the postcentral gyrus of the monkey *Macaca mulatta*. *Bull Johns Hopkins Hosp* 105:108–131.
- Roland PE, Ladegaard-Pedersen H (1977): A quantitative analysis of sensations of tension and of kinesthesia in man. *Brain* 100:671–692.
- Roland PE, Mortensen E (1987): Somatosensory detection of microgeometry, macrogeometry and kinesthesia in man. *Brain Res Rev* 12:1–41.
- Roland PE (1987): Somatosensory detection of microgeometry, macrogeometry and kinesthesia after localized lesions of the cerebral hemispheres in man. *Brain Res* 434:43–94.
- Roland PE, Graufelds CJ, Wählin J, Ingelman L, Andersson M, Ledberg A, Pedersen J, Åkerman S, Dabringhaus A, Zilles K (1994): Human brain atlas, for high-resolution functional and anatomical mapping. *Hum Brain Mapp* 1:173–184.
- Roland PE, O’Sullivan B, Kawashima R (1998): Shape and roughness activate different somatosensory areas in the human brain. *Proc Natl Acad Sci U S A* 95:3295–3300.
- Roland PE, Zilles K (1998): Structural divisions and functional fields in the human cortex. *Brain Res Rev* 26:87–105.
- Romo R, Hernandez A, Zainos A, Salinas E (1998): Somatosensory discrimination based on cortical microstimulation. *Nature* 392:387–390.
- Romo R, Salinas E (1999): Sensing and deciding in the somatosensory system. *Curr Opin Neurobiol* 9:487–493.
- Ruiz S, Crespo P, Romo R (1995): Representation of moving tactile stimuli in the somatic sensory cortex of awake monkeys. *J Neurophysiol* 73:525–537.
- Rymer WZ, D’Almeida A (1980): Joint position sense: the effects of muscle contraction. *Brain* 103:1–22.
- Sakai K, Watanabe E, Onodera Y, Itagaki H, Yamamota E, Koizumi H, Miyashita Y (1995): Functional mapping of the human somatosensory cortex with echo-planar MRI. *Magn Reson Med* 33:736–743.
- Schleicher A, Amunts K, Geyer S, Morosan P, Zilles K (1999): Observer-independent method for microstructural parcellation of cerebral cortex: a quantitative approach to cytoarchitectonics. *Neuroimage* 9:165–177.

- Schnitzler A, Salmelin R, Salenius S, Jousmaki V, Hari R (1995): Tactile information from the human hand reaches the ipsilateral primary somatosensory cortex. *Neurosci Lett* 10:25–28.
- Schormann T, Zilles K (1998): Three-dimensional linear and non-linear transformations: an integration of light microscopical and MRI data. *Hum Brain Mapp* 6:339–347.
- Sur M, Wall JT, Kaas JH (1984): Modular distribution of neurons with slowly adapting and rapidly adapting responses in area 3b of somatosensory cortex in monkeys. *J Neurophysiol* 51:724–744.
- Vallbo ÅB, Hagbarth KE (1968): Activity from skin mechanoreceptors recorded percutaneously in awake human subjects. *Exp Neurol* 21:270–289.
- Werner G, Whitsel BL (1968): Topology of the body representation in somatosensory area I of primates. *J Neurophysiol* 31:856–869.
- Whitsel BL, Dreyer DA, Roppolo JR (1971): Determinants of body representation in postcentral gyrus of macaques. *J Neurophysiol* 34:1018–1034.
- Woods RP, Cherry SR, Maziotta JP (1992): Rapid automated algorithm for aligning and reslicing PET images. *J Comput Assist Tomogr* 16:620–633.
- Warren S, Hamalainen H, Gardner E (1986): Objective classification of motion- and direction- sensitive neurons in primary somatosensory cortex of awake monkeys. *J Neurophysiol* 56:598–622.
- Zainos A, Merchant H, Hernandez A, Salinas E, Romo R (1997): Role of primary somatic sensory cortex in the categorization of tactile stimuli: effects of lesions. *Exp Brain Res* 115:357–360.
- Zhang J, Riehle A, Requin J, Kornblum S (1997): Dynamics of a single neuron activity in monkey primary motor cortex related to sensorimotor transformation. *J Neurosci* 17:2227–2246.