Exp Brain Res (2002) 143:276–285
DOI 10.1007/s00221-001-0994-4

RESEARCH ARTICLE

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# Comparison of brain activity during different types of proprioceptive inputs: a positron emission tomography study

Received: 23 July 2001 / Accepted: 23 November 2001 / Published online: 5 February 2002


**Abstract** It has been shown that the primary and secondary somatosensory cortex, as well as the supplementary motor area (SMA), are involved in central processing of proprioceptive signals during passive and active arm movements. However, it is not clear whether different cortical areas are involved in processing of different proprioceptive inputs (skin, joint, muscle receptors), what their relative contributions might be, where kinesthetic sensations are formed within the CNS, and how they interact when the full peripheral proprioceptive machinery acts. In this study we investigated the representation of the brain structures involved in the perception of passive limb movement and illusory movement generated by muscle tendon vibration. Changes in cortical activity as indicated by changes in regional cerebral blood flow (rCBF) were measured using positron emission tomography (PET). Twelve subjects were studied under four conditions: (1) passive flexion-extension movement (PM) of the left forearm; (2) induced illusions of movements (VI) similar to the real PM, induced by alternating vibration of biceps and triceps tendons (70–80 Hz) at the elbow; (3) alternating vibration of biceps and triceps tendons (with 20–50 Hz) without induced kinesthetic illusions (VN); and (4) rest condition (RE). The results show different patterns of cortex activation. In general, the activation during passive movement was higher in comparison with both kinds of vibration, and activation during vibrations with induced illusions of movement was more prominent than during vibrations without induced illusions. When the PM condition was contrasted with the other conditions we found the following areas of activation – the primary motor (MI) and somatosensory area (SI), the SMA and the supplementary somatosensory area (SSA). In conditions where passive movements and illusory movements were contrasted with rest, some temporal areas, namely primary and associative auditory cortex, were activated, as well as secondary somatosensory cortex (SII). Our data show that different proprioceptive inputs, which induce sensation of movement, are associated with differently located activation patterns in the SI/MI and SMA areas of the cortex. In general, the comparison of activation intensities under different functional conditions indicates the involvement of SII in stimulus perception generation and of the SI/MI and SMA areas in the processing of proprioceptive input. Activation of the primary and secondary auditory cortex might reflect the interaction between somatosensory and auditory systems in movement sense generation. SSA might also be involved in movement sense generation and/or maintenance.

**Keywords** Kinesthesia · Proprioception · Movement · Vibration · Cerebral cortex

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## Introduction

Conscious perception of limb movements depends on proprioceptive information delivered by the full array of specialized muscle, joint and cutaneous afferents. A particular role has long been ascribed to afferent signals arising from muscle spindles (Goodwin et al. 1972; McCloskey 1973; Burke et al. 1976; Roll and Vedel 1982). A similar role was attributed to joint and cutaneous receptors, particularly those situated in the skin around the joints (Goodwin et al. 1972; Hagbarth and

Eklund 1966; Collins and Prochazka 1996; Edin and Johansson 1995). However, the capacity of any individual class of receptor to deliver information about movement and position of the limbs is limited. It rather seems that the presence of the multiple inputs tuned to different aspects of the movement ensure the kinesthetic sensation. In this process, the signals from non-active, stretched muscles antagonistic to the active movers are likely to be more important (Capaday and Cook 1981).

An emerging line of research employing positron emission tomography (PET) and other imaging methods has been directed at linking specific proprioceptive input and its representation in the cerebral structures. In general, these studies showed that conscious perception of limb movements involves both afferent sensory and efferent motor components of cortical motor processing. It has been shown that the primary and secondary somatosensory cortex, as well as the supplementary motor area (SMA), are involved in central processing of incoming afferent signals during passive and active arm movements (e.g., Roland et al. 1980; Dettmers et al. 1995; Weiller et al. 1996; Mima et al. 1999). Weiller and colleagues (1996) showed that passive movements of the elbow are associated with essentially the same pattern of brain activation as the pattern obtained during active movements, the activation involving not only the somatosensory cortex but also the SMA and the motor cortex. However, Mima and colleagues (1999) failed to detect the activation of the sensorimotor cortex during passive movements of the finger, in experiments designed specially to selectively activate proprioception with a minimal contribution from the tactile senses. During illusions of movement induced by muscle vibration eliciting increased afferent activity from muscle spindles, activation of motor areas was found (Naito et al. 1999). At the same time, vibration of the muscle that did not evoke illusions of movement failed to induce significant cortical activation in both motor and somatosensory areas (Naito et al. 1999).

Therefore, the question as to how multiple afferent inputs are combined and where within the CNS the compound signal is generated still awaits systematic investigation, and in particular whether areas involved in processing of proprioceptive inflow and/or generation of movement sense differ during different types of proprioceptive inflow. The interaction between the peripheral afferent input reaching the somatosensory cortex and the neighboring motor output areas is important for understanding how peripheral input can influence the motor commands and execution of movements.

In the present study we investigated the representation of the brain structures involved in the perception of passive flexion-extension limb movements. To discern between proprioceptive input originating from agonist/antagonist pairs of muscles and the overall afferent input, we compared patterns of cortical activation related to passive flexion-extension movements and illusions of flexion-extension movement induced by subsequent vibration of biceps and triceps muscle tendons. To exclude the effects of vibration itself, we contrasted the two conditions mentioned above with the condition during vibration that did not elicit kinesthetic illusions. Therefore, to detect brain areas activated during generation of movement sense evoked by applied vibration, we tried to distinguish the effects of movement per se, effect of vibration (in vibration application of lower frequencies) and effect of movement illusion generated during consecutive high frequency vibration of biceps and triceps muscle.

A preliminary report of these data has been presented elsewhere (Medvedev et al. 2001).

## Materials and methods

### Subjects

We studied 12 healthy, right-handed male volunteers (age 23.5± 7.0 years; mean ± SD) without any previous history of neurological or psychiatric disease and any current medication. All subjects gave their informed consent acknowledging that the employed methods had been clearly explained and understood, allowing them to withdraw from the study at any time without prejudice. All procedures were approved by the Ethics Committee of the Institute of the Human Brain, St. Petersburg, Russia, and in accordance with the Declaration of Helsinki.

### Tasks

Subjects lay supine on the coach of the PET camera, with their head fixed in the head-holder and the ears plugged to prevent them from hearing the sound of the motor and the vibrators. The subject's left forearm was fixed in an especially developed hand-holder, which permitted flexion-extension movements about the elbow joint in the horizontal plane. An angle around 120–140° of elbow flexion was chosen in order to avoid extreme positions of the joint. A torque motor attached to the hand-holder was used to induce passive movements of the forearm. Repeated passive flexion-extension movements of 20° amplitude, starting from 120–140°, were performed for 90 s starting 15 s before the injection of $^{15}O$ water and ending 15 s after the scan. The speed of the motor was adjusted so as to induce 15 flexion-extension movements/min. Subjects were instructed to relax completely and not to interfere voluntarily with the passive movements. During all tests, the subject's right forearm was positioned so as to enable the injection of $^{15}O$-water through a catheter inserted into the right cubital vein.

Two vibrators (V2, Gearing & Watson Electronics Ltd., UK) were attached to the hand-holder such that they contacted the biceps and triceps tendons for consecutive vibration applications while keeping the same position of the forearm in the holder. During vibration, the hand-holder was fixed in the middle position, i.e., 130°, to ensure a maximal effect of vibration (see Roll et al. 1980), and to prevent any movement of the forearm. Special care was taken to adjust the vibrator prodders (tip diameter 1.5 cm), so that they exerted only a light pressure on the skin surface over the tendons, but a good contact with the tendon was ensured. Sinusoidal vibration stimuli at frequencies from 10 to 120 Hz and at amplitudes from 2 to 0.2 mm, respectively, were applied perpendicularly to the tendon. The vibratory signal was displayed on the oscilloscope and kept constant throughout the scan. Vibration was applied for 90 s, starting 15 s before the injection of $^{15}O$ water and ending 15 s after the scan.

In order to produce illusory arm movements, the triceps and biceps tendons were vibrated alternately every 2 s to mimic the timing of passive movement. Before the tests, the frequency and amplitude inducing the strongest illusion of movement, and the maximal frequency and amplitude of vibration not inducing movement

illusions, were determined. The subjects were told that their tendons would be vibrated and that they might feel their forearm move. They were then asked to match the illusory movements with free movements of the opposite hand, trying to match both movement amplitude and speed. The vibration frequency was gradually increased from 10 to 120 Hz in 10-Hz steps, in order to find the optimal one that induced the strongest illusions which matched the speed and amplitude of passive movements. This frequency was then established as the optimal *illusion* frequency (VI). The frequency was then reduced in 10-Hz steps until any movement illusion disappeared completely. It was then decreased by another 10 Hz, and this value was established as the *no illusion* frequency (VN). After the end of each test, the subjects were asked to describe their subjective feeling, in particular during the *illusion* test, whether the quality and/or the intensity of the movement illusion changed during the test, as well as whether the characteristics of illusory movements matched those of passive flexion/extension movements presented previously. The subjects reporting profound changes in movement illusion did not participate in the study.

To standardize the general level of arousal the subjects were asked to perform a simple discriminative visual task during each condition. The subjects calculated the frequency of appearance of one of the three different stimuli presented on the computer monitor. The presentation of the visual stimuli began 20 s prior to the injection of $^{15}$O-water.

In order to establish matching conditions across tests (constant level of background noise), the torque motor was switched on 60 s before the injection, being mechanically disconnected from the holder and not generating any movement except in the passive movement test. The noise from vibrators attached to the forearm was much lower than the noise from the torque motor but distinctly louder when operating without contact with the skin. Therefore, during rest and passive conditions, the vibrators were switched off and the prodders were detached from the arm.

### Conditions in PET

Four conditions were used in random order (two scans per condition amounting to eight scans per subject):

1. Rest condition (RE): The subjects were instructed to relax completely and avoid any movement.
2. Vibration at the frequency not eliciting movement illusions (VN): The frequency not inducing any kinesthetic illusion in each subject (20–50 Hz) was selected.
3. Vibration at the frequency eliciting an illusion of movement (VI): The frequency optimal for eliciting illusion in each subject was applied (70–80 Hz).
4. Passive, motor-generated, flexion-extension movements (PM): Passive flexion-extension movements of the left elbow were carried out.

### Electromyogram recording

Electromyogram (EMG) activity was recorded from biceps and triceps muscles by means of two pairs of surface disposable electrodes (Blue Sensor type Q-10-A, Medicotest, Denmark) placed on the muscle bellies. Signals were amplified within bandwidths of 30–1000 Hz. The AD conversion of the amplified signal was done at a frequency of 1000 Hz/channel (Polyneurograph DK 86, St. Petersburg, Russia). EMG recording began 60 s before the scan. It was carefully checked whether a tonic vibration reflex (TVR) appeared (see Hagbarth and Eklund 1966; Eklund and Hagbarth 1966) during the vibration tests, and whether voluntary activity occurred during passive movements.

### PET data acquisition and analysis

All PET scans were performed by means of a Scanditronix PC2048–15B camera (15 parallel slices with an in-plane spatial resolution of 6.5 mm FWHM in the center of the FOW and an interslice distance of 6.5 mm; for technical details see Holte et al. 1989; Evans et al. 1991). Regional cerebral blood flow (rCBF) was measured with the use of [$^{15}$O]-labeled water and using the autoradiographic method – following an intravenous bolus injection of 50–60 mCi of $H_2{}^{15}O$. A 60-s PET scan was acquired ca. 5–7 s after the bolus injection. The image reconstruction was done using a 7-mm Hanning filter and a measured attenuation correction ($^{68}$Ge/$^{68}$Ga 10-min transmission scan, performed prior the study). Acquired activity was used as an index of CBF due to the near linear relationship between activity distribution and rCBF (Fox and Mintun 1989).

The data were analyzed with SPM 99 software (Friston et al. 1995). Following the realignment of images from each subject to correct for any changes in head position between scans, the images were transformed into standard anatomical space used in SPM 99. In order to increase the signal-to-noise ratio and to accommodate normal variability in functional and gyral anatomy, the images were smoothed with a gaussian filter of 13×13×13 mm width (Worsley et al. 1996). The resulting activity data were normalized for differences in global flow by scaling voxel by voxel to a global mean of 50 ml/dl/min (McIntosh et al. 1996).

Task-specific activations were assessed by statistical comparisons of conditions using *t*-statistics. For the detected activation to be statistically significant, the significance threshold for the resulting statistical parametric maps (SPM*t*) was set at $P<0.05$ in voxel based analysis. In some contrasts, where no activation occurred at voxel level, or if they were very small, we used the cluster-based analysis SPM*t* with thresholds set at $P<0.001$ when uncorrected, and activations were considered significant at $P<0.05$ when corrected at cluster level and at cluster sizes >200. Anatomical identification of activations was made on the basis of the Talairach and Tournoux brain atlas (Talairach and Tournoux 1988), and coordinates obtained in the SPM analysis were converted to the coordinates of the Talairach and Tournoux atlas (for algorithm see http://www.mrc-cbu.cam.ac.uk/imaging).

To elucidate possible different functional roles of areas found in the analysis of contrasts, an additional analysis was performed. We employed the SPM analysis using *F*-statistics (effects of interest) at $P<0.0005$ corrected, revealing the differences between brain areas in different conditions. One of the important steps in SPM analysis is the estimation of the general linear model parameters for every voxel. After parameters are estimated for given voxel, SPM enables the value observed in this voxel for every scan to be split into three parts: one which may be attributed to the parameters of interest (conditions effects in our case), a second one which may be attributed to the parameters of no interest (subjects effects in our case) and a third considered as noise. The first part is known in SPM terms as a "fitted" model response, and the sum of the first and the third as an "adjusted" model response for the voxel under consideration. Averaging the fitted response for all clusters' voxels then enables a comparison of the values of activation in particular clusters by plotting the scattergrams of relative values of activations under all experimental conditions.

## Results

Altogether 12 subjects completed the study and were subsequently included in the analysis. They all reported vivid feelings of flexion-extension movements throughout the trials with a high-frequency vibration stimulation. Nine subjects experienced strong, steady kinesthetic illusion of movement during the scan, which did not differ from the one elicited before the test, while in three subjects the illusion sensation was slightly weaker towards the end of the scan. None of them experienced kinesthetic illusions or any other inconveniences during VN, during passive movements or the resting conditions.

**Table 1** Significant[a] increases in regional brain activity in the right hemisphere obtained in voxel based analysis of PM-RE, VI-RE, VN-RE, PM-VI and PM-VN contrasts

| Contrast and area[b] | Cluster size | *P* corrected for the cluster level | Coordinates of primary local maxima (mm) | | | *P* corrected for the voxel level |
|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | |
| PM-RE | | | | | | |
| 1. G. postcentralis (BA 1, 2, 3), **SI**<br>G. precentralis (BA 4), **MI**<br>G. frontalis medialis (BA 6), **SMA**<br>Lobulus paracentralis (BA 5), **SSA** | 1350 | 0.000 | +12 | –18 | +54 | 0.000 |
| 2. Lobulus parietalis inferior (BA 40), **SII**<br>G. temporalis superior (BA 22, 42), **AA**<br>G. temporalis transversi (BA 41), **AI** | 728 | 0.000 | +48 | –28 | +20 | 0.000 |
| VI-RE | | | | | | |
| 1. G. temporalis superior (BA 22, 42), **AA**<br>G. temporalis transversi (BA 41), **AI**<br>Lobulus parietalis inferior (BA 40), **SII** | 782 | 0.000 | +52 | –30 | +22 | 0.000 |
| VN-RE | | | | | | |
| 1. Lobulus parietalis inferior (BA 40), **SII** | 6 | 0.020 | +46 | –26 | +22 | 0.033 |
| PM-VI | | | | | | |
| 1. G. postcentralis (BA 1, 2, 3), **SI**<br>G. precentralis (BA 4), **MI** | 424 | 0.000 | +44 | –28 | +58 | 0.000 |
| 2. G. frontalis medialis (BA 6), **SMA** | 279 | 0.000 | +12 | –18 | +54 | 0.000 |
| PM-VN | | | | | | |
| 1. G. postcentralis (BA 1, 2, 3), **SI**<br>G. precentralis (BA 4), **MI**<br>G. frontalis medialis (BA 6), **SMA**<br>Lobulus paracentralis (BA 5), **SSA** | 1787 | 0.000 | +14 | –16 | +52 | 0.000 |
| VI-VN | | | | | | |
| Not found | | | | | | |

[a] SPM*t* threshold at $P<0.05$ corrected
[b] Brodmann's areas are given in parentheses

## EMG activity

Across all tests in all subjects, EMG activity was absent in the majority of trials. However, occasionally low-level EMG activity was noticed. Its mean level never reached more than 3% of the mean level of EMG activity during maximal voluntary contractions recorded before the start of testing. It usually occurred during passive movement conditions (PM), indicating that the subjects sometimes interacted with the passive movements generated by the external torque motor. When it occurred, the EMG activity was always present in one muscle, usually the m. triceps brachii, and always followed the passive movement, i.e., was concurrent with the flexion movement, and was never present in more than 5 out of 15 flexion-extension movements. In two subjects, EMG activity was noticed during the VI test. Again it was very low, not exceeding 3% of maximal EMG, random, short lasting and always concomitant with vibration of a particular muscle, never occurring during vibration of the opposite muscle. In those trials, a possible appearance of the TVR can be excluded, by virtue of the usual characteristics of the TVR, with its slow, progressive development (Hagbarth and Eklund 1966; Hagbarth et al. 1976; Gilhodes et al. 1992), which was not noticed in our recordings. Also, arm angles of around 120° were chosen to be in a range where the appearance of the TVR is less likely (Roll et al. 1980), and the relaxed arm would minimize the chance for TVR appearance (e.g., Eklund and Hagbarth 1966). Therefore, we would attribute those EMG appearances as an interaction with illusions of movement.

It can also be assumed that this occasional low-level muscle activation might have caused cortical activation in the VI condition (see later). However, when those two subjects were excluded from the analysis and the data recalculated, no differences in activation were revealed. Therefore, the overall analysis included all 12 subjects.

## PET results

To detect changes of regional brain activity related to the order of scans, an additional analysis was performed. Scans of each subject were grouped according to their numbers in the PET session and the first, second, etc., scan was contrasted with all other scans. This analysis revealed significant (SPM*t* at $P<0.05$ corrected) activa-

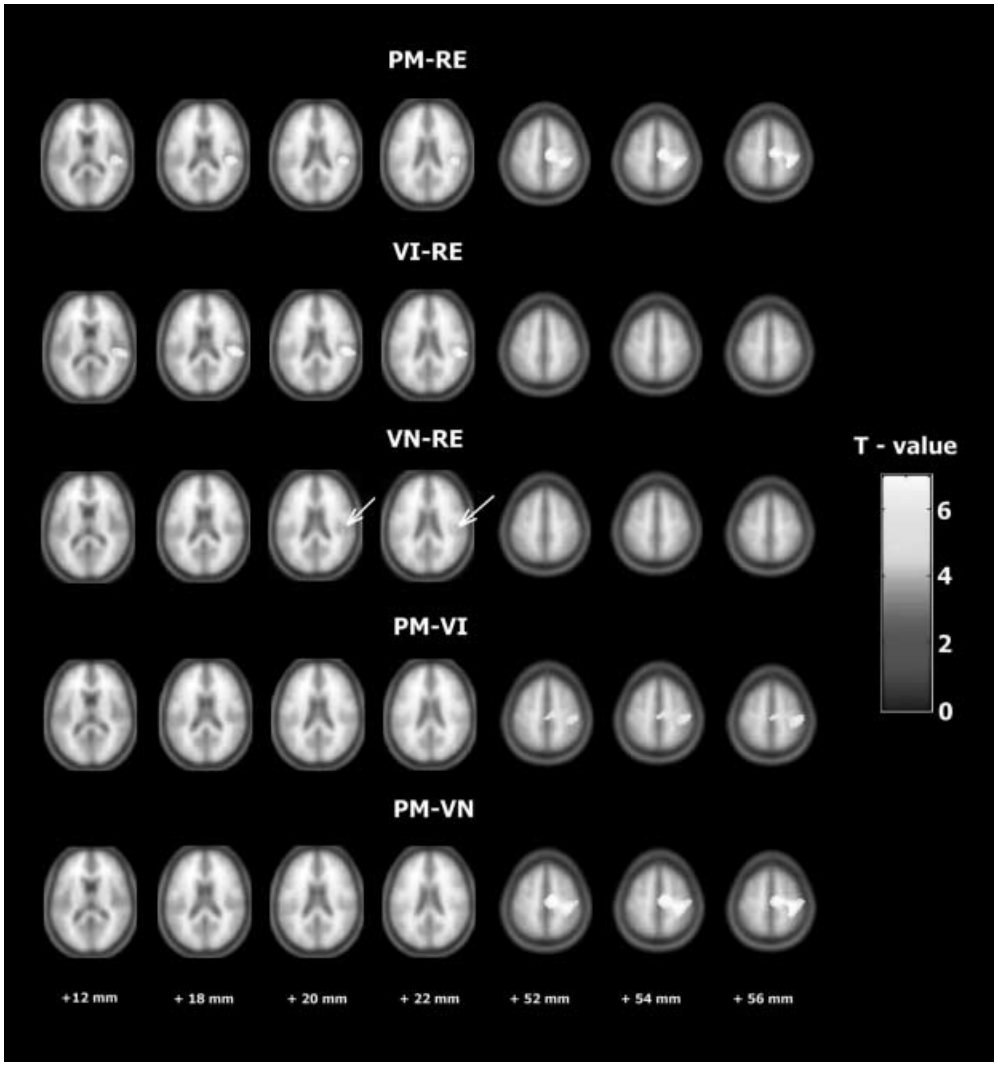


**Fig. 1** Areas of significantly (SPM*t* threshold at $P<0.05$ corrected) activated areas obtained in PM-RE, VI-RE, VN-RE, PM-VI and PM-VN comparisons. The activations are shown as statistical maps that show the areas of regional cerebral blood flow (rCBF) increase with *t*-values coded according to *the color bar shown on the right*. Maps are superimposed on a T1-weighted MRI SPM template image. *The left side of each image* is the left side of the brain. *The numbers at the bottom* indicate the level above the AC-PC line. See Table 1 for anatomical localization of activated areas

tions in the temporal cortex (BA 37) and parietal cortex (BA 40) only when the first scans of the PET sessions were contrasted with the others. Therefore, the first scans were eliminated from the analysis. However, elimination of these scans did not change our results noticeably. It has to be stressed that all subjects experienced kinesthetic illusions during the preparatory procedures, while the optimal vibration frequencies were established. In spite of that, the fact that rCBF increases in temporal (BA 37) and parietal cortex (BA 40) were obtained only in the first scan, and not in all other subsequent scans, might be related to novel conditions when the PET scanning procedure was introduced. Temporal and parietal regions including BA 37 were previously shown to participate in a novelty encoding network (e.g., Tulving et al. 1994, 1996). Bartlett and colleagues (1988) and Stapleton and colleagues (1997) also reported differences in regional activity between the first and second PET sessions. The authors attributed these differences to different levels of anxiety that might be considered as part of a reaction to the novel situation. We believe that our subjects reacted in a similar manner when the "real" PET procedure started.

All brain activations found were located in the right (contralateral) hemisphere.

Initially, six contrasts were analyzed – PM-RE, VI-RE, VN-RE, PM-VN, PM-VI and VI-VN. Voxel-based analysis revealed significant rCBF changes in five contrasts: PM-RE, VI-RE, VN-RE, PM-VN and PM-VI (Table 1, Fig. 1).

The comparison of passive movement (PM) with other conditions (contrasts PM-VI, PM-VN, PM-RE) showed similar localizations of the rCBF increases in primary motor area, MI [Brodmann's area (BA) 4]; supplementary motor area, SMA (BA 6); and primary somatosensory area, SI (BA 1, 2, 3). In PM-RE and PM-VN contrasts, areas of increased rCBF extended to the supplementary sensory area – SSA (BA 5). In addition, in the PM-RE contrast, increases in rCBF were found in the secondary somatosensory cortex, SII (BA 40); the auditory cortex, primary, AI (BA 41); and the associative, AA (BA 22, 42).

Vibration with illusion of movement (VI) contrasted with RE (contrast VI-RE) demonstrated increases in rCBF in SII (BA 40) and the auditory cortex – AI

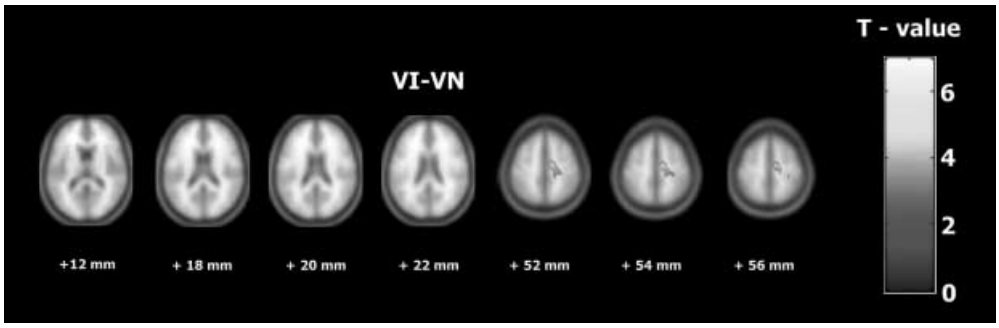


**Fig. 2** Areas of significantly (SPM*t* threshold at $P<0.001$ uncorrected) activated areas obtained in VI-VN comparison. All areas shown are significant at $P<0.05$ corrected at cluster level and cluster size >200. The activations are shown as statistical maps that show the areas of regional cerebral blood flow (rCBF) increase with *t*-values coded according to *the color bar shown on the right*. Maps are superimposed on a T1-weighted MRI SPM template image. *The left side of each image* is the left side of the brain. *The numbers at the bottom* indicate the level above the AC-PC line. See Table 2 for anatomical localization of activated areas

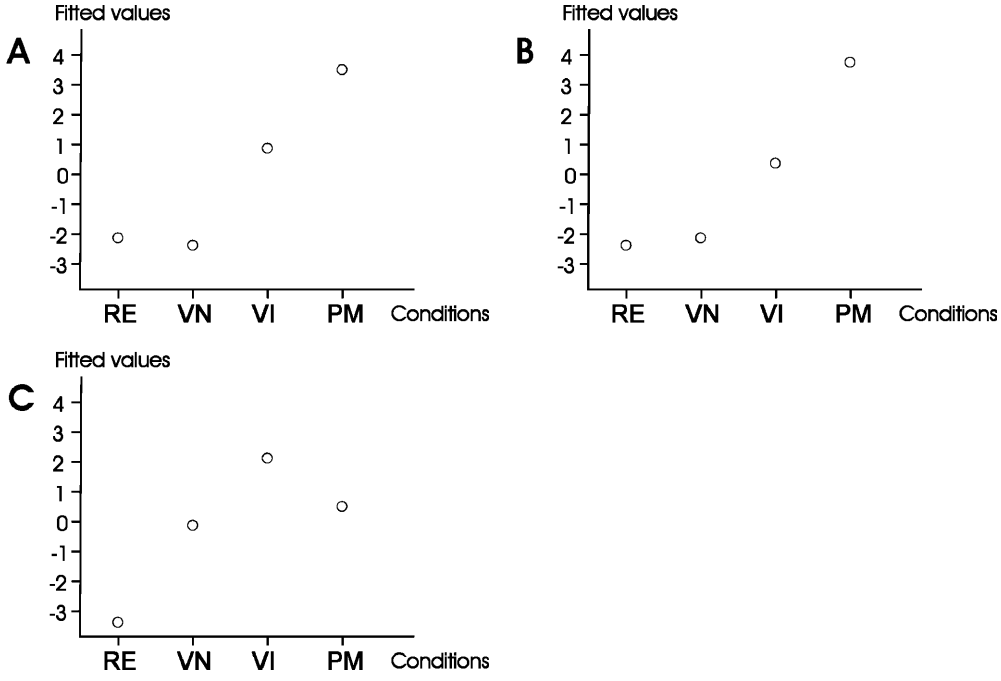


**Fig. 3** Scattergrams of "fitted responses averaged on each cluster" – "conditions" (see "Materials and methods" for detailed description). *Scattergram A* represents cluster 1 in Table 3 – SMA and SSA; *B* represents cluster 2 of the same table – SI and MI areas; and *C* represents cluster 3 in Table 3 – SII, AA and AI areas

**Table 2** Significant[a] increases in regional brain activity in right hemisphere obtained in cluster based analysis of VI-VN contrasts

| Contrast and area[b] | Cluster size | *P* corrected for the cluster level | Coordinates of primary local maxima (mm) | | | *P* corrected for the voxel level |
|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | |
| VI-VN | | | | | | |
| 1. G. precentralis (BA 4), **MI**<br>G. frontalis medialis (BA 6), **SMA** | 439 | 0.002 | +14 | –12 | +54 | 0.099 |

[a] SPM*t* threshold at $P<0.001$ uncorrected and cluster size >200 voxels; clusters with corrected $P<0.05$ at cluster level were considered as significant

[b] Brodmann's areas are given in parentheses

(BA 41) and AA (BA 22, 42). In VN-RE contrast, an increase in rCBF was found in SII (BA 40) only.

As the voxel-based analysis revealed no suprathreshold clusters in VI-VN contrast, the cluster-based analysis was applied for this comparison. In VI-VN contrast, clusters of rCBF increases were found in primary motor area, MI (BA 4); and supplementary motor area, SMA (BA 6) (Table 2, Fig. 2).

*F*-statistic analysis (effect of interest) revealed three different clusters. These clusters are equivalent to those

**Table 3** Significant[a] differences between all conditions obtained in the study using *F*-statistic analysis representing effects of interest (experimental conditions)

| Area[b] | Cluster size | Coordinates of primary local maxima (mm) | | | *P* corrected for the voxel level |
|---|---|---|---|---|---|
| | | *x* | *y* | *z* | |
| 1. G. frontalis medialis (BA 6), **SMA**<br>Lobulus paracentralis (BA 5), **SSA** | 227 | +12 | –14 | +52 | 0.000 |
| 2. G. postcentralis (BA 1, 2), **SI**<br>G. precentralis (BA 4), **MI** | 106 | +32 | –32 | +56 | 0.000 |
| 3. Lobulus parietalis inferior (BA 40), **SII**<br>G. temporalis superior (BA 42), **AA**<br>G. temporalis transversi (BA 41), **AI** | 124 | +54 | –26 | +16 | 0.000 |

SPMFs were thresholded at $P<0.0005$ corrected
[b] Brodmann's areas are given in parentheses

appearing in contrasts. See Table 3 for a detailed description of each particular cluster.

Scattergrams ("fitted responses averaged on each cluster" – "conditions"), showing relative values of activation under different conditions, are given in Fig. 3.

In these scattergrams two different patterns can be seen. In the first two diagrams (A and B), related respectively to the first two clusters located in SMA, SSA, SI and MI areas, a similar activation between RE and VN conditions was found. The third diagram (C), related to the cluster located in SII, AA and AI areas, shows a small difference in activation between PM and VI conditions.

## Discussion

Our data show different patterns of brain activation in different experimental conditions. Activation during passive movements was significantly higher in comparison with both kinds of tests with applied vibrations, and activation during vibration with induced illusions of movement was more prominent than during vibrations without illusion effects.

Passive movements contrasted with the rest condition showed involvement of the contralateral SI, MI, SMA, SSA, and also of SII and the auditory cortex (Table 1, Fig. 1). An involvement of the contralateral sensorimotor cortex (SI/MI), SMA and inferior parietal cortex during passive movement, as related to the processing of afferent information, was described previously (Weiller et al. 1996). But in some studies widely distributed activation was reported only during active movements, while the brain representation of passive movements was limited to SI and SII only, and did not extend to SMA, where it could have been expected, since the SMA receives inputs from proprioceptors (i.e., Mima et al. 1999). The authors suggested that the response of the SMA during the passive movement could have been too small or temporally transient, due to a small number of activated receptors during single finger movement so that the sensitivity of the PET was insufficient to reveal the activation (Mima et al. 1999). By contrast, in our study, the large elbow movements likely activated more receptors and thus produced a greater proprioceptive inflow. Also, all three separate clusters in Table 3 and Fig. 3 show activation during passive movement. This further supports the interpretation that areas SI, MI, SMA and SSA were activated in the PM condition in which proprioceptive input exists.

The aforementioned findings are in line with the general opinion about the role of SI, MI and SMA in processing of proprioceptive input and in the generation of the movement sense. Further support for a role of these areas in processing of incoming afferent information comes from the study of Reddy and colleagues, which showed the total absence of cortical activation during passive movements performed in patients with severe distal sensory neuropathy (Reddy et al. 2001). This further emphasizes the dependence of cortical activation during passive movements on sensory inflow.

The comparison of passive movements with vibratory conditions, with or without illusions of movement, showed similar activated areas (SI, MI, SMA), except for the auditory cortex and SII. This is again in line with earlier findings about the role of sensorimotor areas in proprioceptive information processing (Weiller et al. 1996). But in our study the activation of the supplementary sensory area, SSA, was present only when a sense of movement existed (during passive movements). It was not present in the PM-VI comparison, both conditions containing a sense of movement. It is possible that SSA was activated in both PM and VI conditions, and consequently eliminated by the analysis. This could support the role of SSA in the generation and/or maintenance of movement sense.

Vibration with or without induced illusions of movement contrasted with the rest condition activated SII only, not MI, SI or SMA. Higher-frequency vibration that induced illusory movements also activated areas in the temporal lobe (auditory cortex – AA, AI). Data published by Naito and colleagues (1999) suggest that the SMA, CMAc (caudal cingulate motor area), PMd (dorsal premotor cortex) and area 4a are specifically associated

with the experience of kinesthetic illusions. In our study we did not see an activation of those structures during vibratory conditions. Naito and colleagues (1999) also reported the activation of the parietal operculum (SII) during vibration when the illusion was contrasted with rest, but not when it was contrasted with vibration without illusion. They concluded that this somatosensory region is likely not engaged in the generation of kinesthetic illusions. Area SII has been previously suggested to be involved in processing of discriminative somatosensation (Seitz and Roland 1992; Coghill et al. 1994), in relation to passive movements (Weiller et al. 1996), as well as in coding of precise aspects of movements (Lacoboni et al. 1999). However, in our study, activation of SII was observed in both conditions with applied vibration, as well as during passive movement. Similarly, Fox and colleagues (1987) and Burton and colleagues (1993) both reported activation of the parietal operculum during 130-Hz vibrations. All that could indicate that SII is not involved in the generation of movement sense, but rather in the processing and perception of peripheral, proprioceptive stimuli, either "natural" (passive movement) or "artificial" (applied vibration). Our findings support the notion that SII is the common end-point for vibratory sensory inflow, where the sense of the peripheral stimulus could be processed and generated. However, in our study, when an illusion of movement was induced by high-frequency vibration, the auditory cortex was also activated. This indicates that the illusions of movement and the sense of vibrations (as a peripheral stimulus) were maintained by different patterns of brain activation. Therefore, our data suggest that both passive movements and illusions of movement activate some identical areas (SII, AA and AI), where the percept of movement could be generated.

Passive movements activate other areas as well (SI, MI, SMA, SSA), apart from temporal areas and SII. Larger cortical activation in passive movements could result from larger spreading of proprioceptive information and/or inflow from other peripheral receptors that are activated by movement per se (cutaneous, joint, other muscle receptors). That is not the case during specific vibration of stationary arm and consecutive selective activation of muscle spindle afferents, mostly primaries (e.g., Goodwin et al. 1972; McCloskey 1973; Burke et al. 1976; Roll and Vedel 1982).

An unexpected finding deserving particular attention was that in some of the conditions (PM and VI contrasted vs RE), the primary auditory cortex (BA 41) and the auditory association cortex (BA 22, 42) in the contralateral temporal lobe were activated. This activation cannot be regarded as a response to noise. First, auditory stimuli activate the auditory cortex bilaterally, while we saw only unilateral activation in the right hemisphere. Second, during the tests, the motor remained switched on during all conditions, including rest, and in this situation subtraction as a step in data processing eliminates all consequences of noise. It appears more likely that it occurred due to interactions between the somatosensory and auditory systems. Evidence for such interactions was previously adduced in several studies (Szczepaniak and Moller 1993; Makeig et al. 1996; Levanen et al. 1998; Jousmaki and Hari 1999; Foxe et al. 2000), where somatosensory stimulation evoked responses not only in SI and SII, but also in the temporal cortex adjacent to the sulcus lateralis, as was the case in our study. Previously, Roland (1982) demonstrated the existence of similar interactions with the $^{133}$Xe intracarotid technique. Altogether, these data indicate that auditory cortex might be involved in processing afferent information and contribute to somatosensory integration processes. In our study, the auditory cortex was activated only in conditions where the sense of movement existed, irrespective of the existence of real movement, i.e., in passive and vibratory illusion conditions (see Table 1). No auditory cortex activation occurred in the VN condition. The activation of the contralateral temporal lobe in the VI condition might be connected with the existence of illusory flexion/extension movement throughout the whole PET recording, which was induced by alternating vibration of biceps and triceps muscle, unlike previous studies in which the illusion of movement was induced only in one muscle by continuous vibration (e.g., Naito et al. 1999). The first two diagrams (A and B) of Fig. 3, related respectively to the first two clusters located in SMA, SSA, SI and MI areas, show similar activations in RE and VN conditions. The third diagram (C), related to the cluster located in SII, AA and AI areas, shows no difference in activation between PM and VI conditions. Altogether, these data indicate that the auditory cortex might be involved in processing afferent information and contribute to somatosensory integration processes and in the generation of movement sense. However, the involvement of the primary and associative auditory cortex in somatosensory integration requires further elucidation.

In the VI-VN contrast, only the MI and SMA areas appeared activated (Table 2, Fig. 2). Since the sense of movement is present only during higher-frequency vibration, it could be expected that additional cortical activation appearing during induced illusions of movement would disclose the cortex site responsible for that process. We found only MI and SMA areas activated, not more. Naito and colleagues (1999) also did not describe activation of areas possibly responsible for the generation of the illusion of movement when they contrasted vibratory trials with rest. Since vibratory inflow from both flexor and extensor muscles was lasting throughout the scan, a possible explanation could be that processing of strong muscle spindle afferent vibration inflow overwhelms subtle additional changes in brain activity for those two vibratory conditions. A similar, profound influence on cortex activation, which was elicited by a similar strong proprioceptive input from muscle spindles, has been described previously (Brooke et al. 1997; Staines et al. 2001).

The activation of additional areas with higher vibration frequencies might partly reflect the vibration frequency difference. However, we believe that this is not

the case since VI-VN contrast shows activation of other areas than those activated by low-frequency vibration only. If the difference in activation were only quantitative, it would be reasonable to assume that higher-frequency vibration would expand the area which was initially activated (SII), instead of activating other brain areas (separate clusters), which was the case here. Also, the well-known characteristics of high-frequency vibration of muscles and tendons (this vibration triggers muscle spindles to fire synchronously with the frequency of applied vibration and generates movement illusions) render it more reasonable to consider the additionally activated areas as functionally different structures, and not as places to which the higher vibratory inflow spreads. For the low-frequency vibration chosen here, it was shown that it triggers muscle spindles to follow that frequency, although not yielding any movement sensation (e.g., Goodwin et al. 1972; McCloskey 1973; Burke et al. 1976; Roll and Vedel 1982).

On the basis of our results, it is difficult to draw consistent conclusions about quantitative or qualitative differences in brain responses to different vibration patterns. On the one hand, the clusters of activation presented in Table 1 are similar, but differ in size. That would support the view of quantitative differences among responses of different vibratory frequencies. However, additional clusters revealed by cluster analysis in Table 2 speak in favor of qualitative differences.

We did not see activation of structures "traditionally" present in PET movement studies – insula or cingulate cortex (Mishkin 1979; Seitz and Roland 1992; Burton et al. 1993; Coghill et al. 1994; Dettmers et al. 1995; Naito et al. 1999, 2000). Activation of the insular cortex, a region heavily linked with both the somatosensory (e.g., Mishkin 1979) and the limbic system, was mentioned mostly in vibration studies with illusion (Naito et al. 1999) as well as without illusions (Seitz and Roland 1992; Coghill et al. 1994; Burton et al. 1993). But in our study we did not find insular-cortex activation in any of the conditions. In some studies, the SMA activation extended into the cingulate cortex, a site predominantly activated by simple movements of the hand (Dettmers et al. 1995; Naito et al. 2000). Since we avoided any active movements in our paradigm, the lack of cingulate activation is not surprising. Another reason could be that in our study subjects performed a visual discrimination task distracting the attention from stimulation of the forearm. It was previously reported that attentive behavior modulates the physiological response of those cortical areas to sensory stimulation: distraction of attention diminishes the response, and focusing enhances activity (Meyer et al. 1991; Forss et al. 1996, Johansen-Berg et al. 2000). Therefore, the lack of activation in cingulate and insular cortices might be due to the lack of explicit somatosensory attention.

In conclusion, perception of passive flexion/extension movements and illusions of movements are associated with different patterns of brain activation. Increase in rCBF in SI/MI and SMA was observed only in response to passive movement encompassing multiple peripheral sensory input. On the other hand, both the perception of passive movements and the perception of illusory movements induced by tendon vibration activated areas in parietal and temporal lobe (SII, AA, AI). The comparison of activation intensities under different functional conditions indicates the involvement of SII in stimulus perception generation and of the SI/MI and SMA areas in the processing of proprioceptive input. Activation of the primary and secondary auditory cortex might reflect the interaction between the somatosensory and auditory systems in movement sense generation. The supplementary somatosensory area (SSA) might also be involved in movement sense generation and/or maintenance.

**Acknowledgements** Special thanks are due to Dr. Uwe Windhorst for his valuable scientific comments and English language improvements of the text. This work was supported by the Swedish Council for Work Life Research.

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