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Effects of stimulus rate on regional cerebral blood flow after median nerve stimulation

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Summary

The primary motor cortex and supplementary motor area (SMA) are purportedly involved in the generation of the P22 and N30 components of somatosensory evoked potentials (SEPs) evoked by electrical stimulation of the median nerve at the wrist. We used regional cerebral blood flow (rCBF) measurements and PET in 10 normal subjects to study the cerebral areas activated by median nerve electrical stimulation. PET scans were performed with the subjects at rest and during stimulation of the right median nerve at frequencies of up to 20 Hz. Stimulation evoked a single focus of activation in the primary somatosensory area (SI). An increase of rCBF in this area was linearly correlated with stimulus frequencies of up to 4 Hz and then reached a plateau. The SMA was not significantly activated by stimulation at any of the frequencies tested. In contrast to the SI, the SMA showed no trend toward a correlation between the rCBF changes and the stimulus repetition rate. In order to achieve maximal resolution in the sensorimotor cortex, regions of interest were placed in individual co-registered MRI–PET images on both sides of the central sulcus. There was no significant increase of rCBF in the crown of the precentral gyrus. These results suggest that a contribution of the primary motor cortex and the SMA to the generation of the P22 and N30 components of SEPs is unlikely. Consequently, functional clinical interpretations derived from P22 or N30 abnormalities must be reconsidered.

Keywords: somatosensory evoked potentials; PET; movement disorders; primary somatosensory area

Abbreviations: ANCOVA = analysis of covariance; rCBF = regional cerebral blood flow; SEP = somatosensory evoked potential; SI = primary somatosensory area; SMA = supplementary motor area; SPM = statistical parametric maps

Introduction

Noninvasive electrophysiological studies of the somatosensory afferent pathways are commonly performed in humans with electrical stimulation of peripheral nerves. The SEPs obtained after such stimulation can be used to detect functional alterations at different levels of the somatosensory pathways and constitute a tool in clinical practice (Cracco and Cracco, 1976; Anziska and Cracco, 1980; Jones *et al.*, 1980; Mauguière and Ibáñez, 1985; Emerson and Pedley, 1986; Yamada *et al.*, 1986; Turano *et al.*, 1991; Ibáñez *et al.*, 1992). However, multiple and controversial hypotheses about the cortical generators of SEP components obtained after median nerve stimulation often make the pathophysiological interpretation of abnormalities in patients confusing. It is agreed that the N20 is the first cortical response of the somatosensory cortex (Allison *et al.*, 1980; Deiber *et al.*, 1986), but there are disagreements about subsequent potentials, particularly the so-called frontal SEP components that are recorded over the central and frontal regions. Some investigators (Goff *et al.*, 1977; Allison *et al.*, 1980, 1991, 1992; Wood *et al.*, 1985) contend that the SI accounts for the generation of all early SEP components (latency of 20–45 ms). Others hold that the P22 and N30 SEP components originate in the frontal cortex (Desmedt and Cheron, 1981; Mauguière *et al.*, 1983; Desmedt and Bourget, 1985; Rossini *et al.*, 1989). One of these components, the N30, is recorded with a maximal amplitude over the frontal part of the scalp

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and is markedly reduced when movement is present (Cheron and Borenstein, 1987; Cohen and Starr, 1987). The SMA has been proposed as the generator of this component (Desmedt and Bourget, 1985; Rossini *et al.*, 1989).

Although movement disorders are not generally associated with sensory deficits, the study of the integrity of somatosensory pathways by recording SEPs in patients with these disorders has become common. Results of studies on the N30 amplitude in hyperkinetic and hypokinetic syndromes in some movement disorders are controversial. In patients with Parkinson's disease or progressive supranuclear palsy, the frontal SEP components, and mainly the N30 potential, are reduced in amplitude (Rossini *et al.*, 1989, 1993; Abbruzzese *et al.*, 1991; Rossini *et al.*, 1993) or unaltered (Mauguière *et al.*, 1993). The amplitude of N30 is also reduced in Huntington's disease (Abbruzzese *et al.*, 1990*a*; Töpper *et al.*, 1993) and increased in hemidystonia (Reilly *et al.*, 1992). Dysfunction of the SMA and the basal ganglia in sensorimotor processing has been hypothesized from these SEP findings (Rossini *et al.*, 1989; Töpper *et al.*, 1993).

Despite their excellent temporal resolution, EEG techniques lack sufficient spatial resolution to answer the question of intracranial SEP generators and, in particular, whether the SMA neurons can be activated by a somatosensory stimulus such as that used to elicit SEPs. Better spatial resolution can be obtained with intracranial recordings, but these studies are difficult to perform and restricted to patients undergoing surgical interventions (Wood *et al.*, 1988; Allison *et al.*, 1991, 1992).

PET offers the opportunity to study the activation of cerebral structures within a few millimeters of spatial resolution. Functional studies with PET are usually performed by measuring the distribution of radioactivity in brain tissue after the injection of ^{15}O-labelled water, which represents an index of rCBF (Fox and Mintun, 1989) and, therefore, an indirect measurement of neuronal activity (Raichle, 1986).

In the present study, we used PET to identify the cortical areas activated during electrical stimulation of the median nerve at the wrist to obtain some insight into the generation of SEP components. We focused on the activity of the primary motor cortex, SMA and parietal SI in response to somatosensory stimuli similar to those used in routine clinical evaluation of SEPs. Further, we studied the modulation of the activity in these areas to different stimulus frequencies, as well as the relationship between modulation and evoked SEP response changes.

Methods

We performed PET and SEP recordings on different days in 10 healthy male volunteers (mean age 30.6±5.02 years), who had normal neurological examinations. The protocol was approved by the Institutional Review Board, and all subjects gave their written informed consent for the study.

PET scans

Regional cerebral blood flow was measured by the distribution of the cerebral radioactivity in a 60-s PET scan following the intravenous bolus injection of 30 mCi of ^{15}O-labelled water. Each subject had five consecutive scans performed at 10-min intervals, one while the subject was at rest, and the others during 0.2, 1, 2 and 4 Hz electrical stimulation of the the right median nerve at the wrist (same procedure as used for SEP recording described below). A subgroup of six subjects had five additional scans during 8, 10, 12, 16 and 20 Hz electrical stimulation of the right median nerve at the wrist. Although it is unusual to perform somatosensory stimulation at frequencies above 4 or 5 Hz, the subjects did not report any pain, but three of them felt some discomfort with both 16 and 20 Hz stimulus frequencies. The order of the scans was pseudorandomized. The maximal dose of radiotracer received by a subject was 300 mCi.

The PET scanning was done with a Scanditronix (Uppsala, Sweden) PC-2048 tomograph yielding 15 simultaneous planes with a slice thickness of 6.5 mm. A transmission scan performed at the beginning of each session and obtained with a rotating ^{68}germanium/^{68}gallium source allowed correction for attenuation effects. The subjects lay supine with their eyes and ears covered. Stimulation of the median nerve was started ~10 s before the injection of ^{15}O-labelled water. The scan automatically started ~10 s after the injection when a sufficient number of counts were detected, indicating the arrival of the radiotracer to the brain. Images were reconstructed with a final voxel size of 2×2×6.5 mm. The 15 original planes were linearly interpolated to 43 to obtain approximately cubic voxels. The integrated counts measured during the 60-s scan were used as an index of rCBF.

MRIs

A volumetric high-resolution MRI was obtained from each subject with a 1.5-Tesla system using a T_1-weighted gradient-echo sequence [repetition time (TR) of 33 ms; echo time (TE) of 5 ms; flip angle (FA) of 33°] with matrix size of 512×512 and a 31-cm field of view. After reconstruction and interpolation, the final voxel size was 2 mm^3.

Recording methods

Subjects lay comfortably in a reclining chair in a semi-darkened room with their eyes closed. The SEPs were recorded with a Synamp data acquisition system (Neuroscan, Inc., Herndon, Va., USA). The right median nerve at the wrist was electrically stimulated at an intensity three times the sensory threshold, which exceeded the motor threshold for the abductor pollicis brevis muscle. The stimulus intensity, which ranged from 6 to 9 mA, was constant for each subject. The cathode was situated proximal to the anode. The stimulus consisted of a 0.2 ms electrical square-wave pulse delivered through surface disk electrodes.

The EEG was recorded with 30 silver chloride electrodes affixed to the scalp with a conductive gel. The electrodes were referenced to the ear lobe ipsilateral to the side stimulated (Tomberg *et al.*, 1991). Twenty of these electrodes were placed according to the international 10–20 system of electrode placement. Each of the remaining 10 electrodes was placed equidistant between two of those situated at the standard position. One additional bipolar derivation was used to record the electrooculogram. Impedances were kept below 5 kΩ.

The signal was amplified and digitized. Then, an on-line digital filter with a band-pass from 2 to 500 Hz (–3 dB cutoff points, roll-off 24 dB per octave) was applied to individual epochs. An average of 600–1000 of these epochs was used for calculations. Analysis time was set to 450 ms (150 ms pre-stimulus, 300 ms post-stimulus) for the stimulus frequencies of 0.2, 1 and 2 Hz, and to 240 ms (40 ms pre-stimulus, 200 ms post-stimulus) for the stimulus frequency of 4 Hz (bin width of 0.5 ms).

Analysis of data

For analysis of the PET data, calculations were performed on SPARC computers using ANALYZE version 6.1 image display software (BRU, Mayo Foundation, Rochester, Minn., USA) and PROMATLAB version 3.5 (Math Works, Inc., Natick, Mass., USA). Statistical parametric maps (SPM) of significant blood flow changes were obtained using SPM software (MRC Cyclotron Unit, London), which accounts for stereotaxic anatomical standardization, analysis of covariance (ANCOVA), and *t* statistics (Friston *et al.*, 1989, 1990, 1991). All PET scans were transformed into the standard anatomical space (Talairach and Tournoux, 1988) and, therefore, reconstructed parallel to the intercommissural (AP–PC) line. The voxel size after reconstruction was 2×2 mm with an interplane distance of 4 mm. A Gaussian kernel filter of 20×20×12 mm was applied, resulting in smoothing of the data, which increases the signal-to-noise ratio of the images. An ANCOVA of regional versus global CBF was performed on a pixel-by-pixel basis to obtain mean rCBF values and their variance. The global CBF value was adjusted to 50 ml/dl/min. Finally, SPMs were generated using *t* statistics transformed to a normal distribution, with significance defined as $P < 0.05$ with a Bonferroni-type correction.

Discrimination of the activity in the primary motor and somatosensory cortices was accomplished by performing a regions of interest analysis for each subject without stereotaxic normalization of brain activity or filtering of the PET images. Automated Image Registration software (Woods *et al.*, 1992, 1993), which allows the alignment of functional images (MRI and PET) between or across modality, was used to align the MRI scan to the 10 PET scans of each subject. First, an average of the 10 interpolated PET scans was obtained by realigning all 10 PET images to one of them. Secondly, the MRI scan was aligned to the averaged PET image. Normalization of the global rCBF to 50 ml/dl/min was performed on the aligned PET images, but did not include an ANCOVA. To detect the planes where the central regions were activated for each individual, a difference PET scan of the rest condition to the 4 Hz stimulus condition was computed. The plane with the largest difference value, and two planes below and two planes above it, were selected for regions of interest analysis. In the MRI scans, the central sulcus was identified from sagittal slices (Talairach and Tournoux, 1988; Steinmetz *et al.*, 1989) and then four regions of interest of 4×6 mm were placed in the transverse MRI scan: one at the precentral gyrus, corresponding to the most lateral part of the motor cortex, one at the postcentral gyrus (areas 1 and 2 of the primary parietal cortex) and two on the central sulcus, where the motor and somatosensory cortex are close to each other. Finally, these regions of interest were translated to the PET images to measure the normalized rCBF values. For each region of interest, an average of the rCBF values of the selected five planes was obtained.

For the SEP analysis, the P22, P24 and P27 components were not analysed because of the confusion that exists about their nomenclature. Instead, attention was focused on the early components (N20, N30, P45) and the late components (N70, N135) of the SEPs. After the traces from the individual epochs were averaged, the amplitudes of the components were measured from baseline to peak. A Friedman nonparametric test of the amplitudes for each stimulus rate was carried out and, if significant, was followed by a Wilcoxson paired nonparametric test for each component between amplitudes obtained with a different stimulus rate.

Results

PET experiment

In the 10 subjects who had median nerve stimulation at 0.2, 1, 2 and 4 Hz, there was a significant increase of activity at the last two frequencies compared with the rest condition (Fig. 1). The stereotaxic coordinates of the activated area, as well as the *Z* value at the maxima for each stimulus frequency, are shown in Table 1. These coordinates correspond to the SI in the atlas of Talairach and Tournoux (1988).

Although stimulus frequencies of 0.2 and 1 Hz failed to elicit any significant increase of activity, at 1 Hz there was a well-defined area (Fig. 1B) for which the *Z* values were close to the threshold level for significance. In contrast, no significant activation of the SMA occurred at any of the stimulus frequencies used, and the *Z* values were well below the threshold for significance (Fig. 1 and Table 1). An omnibus test with the threshold set to $P < 0.05$ did not detect SMA activation either. This test, however, detected the activation of other pixels located in the white matter and also on the boundaries of the brain corresponding to border effect artifact. This threshold level can introduce type I statistical errors, and for this reason, we will not discuss these results further.

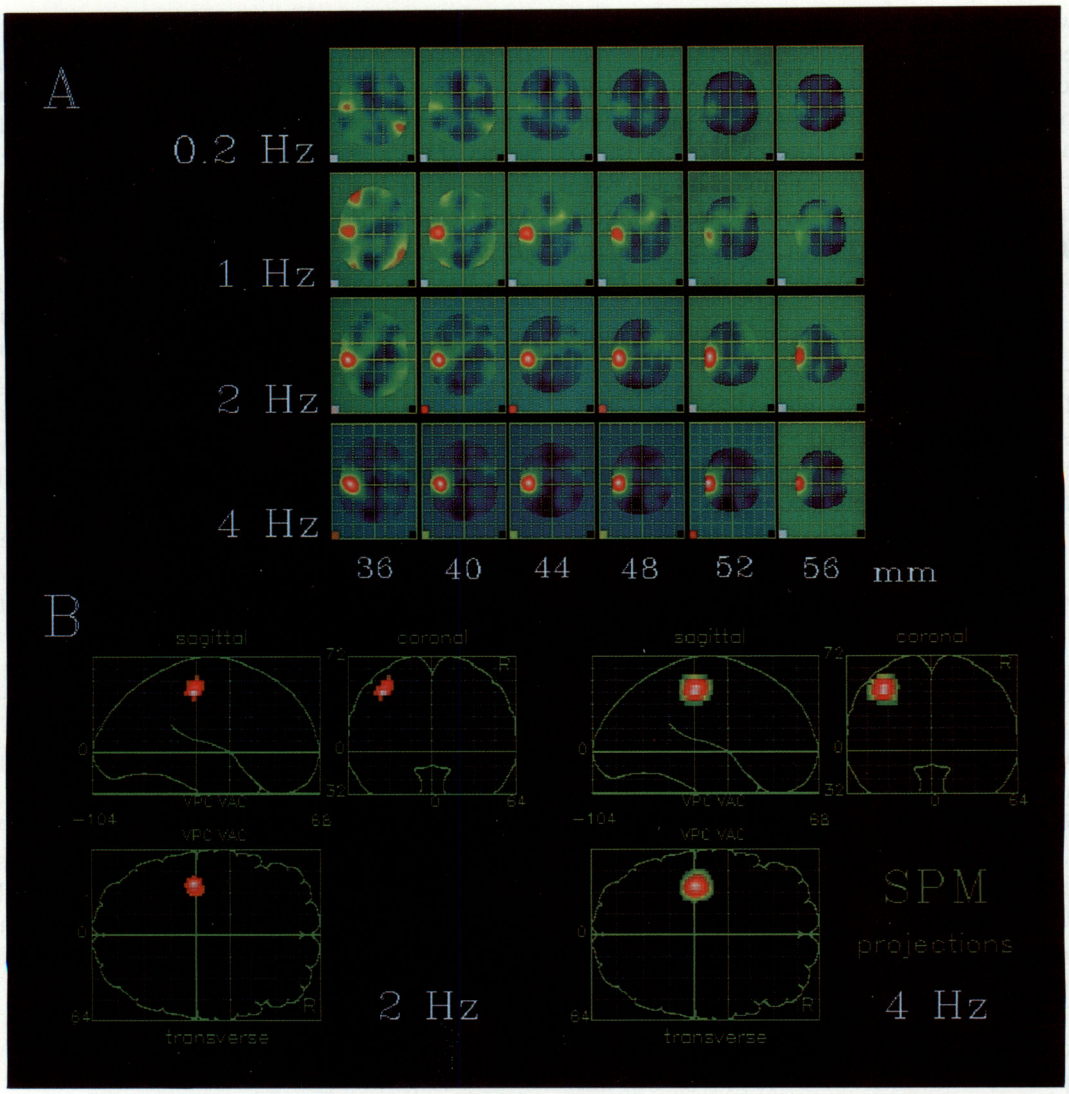


Fig. 1 (**A**) $SPM_{\{t\}}$ values obtained for the 0.2, 1, 2 and 4 Hz stimulus rates used in the 10 subjects. The planes cover from 36 to 56 mm above the AC–PC line. The *Z* values are represented on the arbitrary colour scale, ranging from low (blue, green) to high (red, white), and each plane is scaled to its maximum *Z* value. The coloured square on the bottom left of each plane indicates the significance level for that plane. The maps for only the 2 and 4 Hz stimulus rates show values above the threshold. For the 1 Hz stimulus rate, the *Z* values define an area similar to that for the 2 and 4 Hz rates; however, these values are below the threshold. (**B**) Orthogonal projections of the statistical comparisons between 2 and 4 Hz stimulation of the median nerve versus the rest condition in the 10 subjects. Only the somatosensory cortex is significantly activated.

In the subgroup of six subjects in whom stimulus frequencies of up to 20 Hz were used, significant activation in the SI also occurred at each frequency (Fig. 2). The position of the most significant pixel varied slightly between different stimulus frequencies (Table 1). Interestingly, for the 20 Hz stimulus, an additional area in the depth of the sylvian fissure showed a significant increase of activity (Table 1).

Adjusted rCBF values for each subject in the SI for the rest condition and the different stimulus frequencies are shown in Figs 3 and 4. There was a progressive, linear increase of adjusted rCBF from the rest condition up to the 4 Hz stimulus frequency, where the increase became maximal and then reached a plateau or slowly decreased.

The adjusted rCBF values calculated at two different localizations of the SMA, anterior and posterior to the AC line, or Vca of the atlas of Talairach and Tournoux (1988), did not follow the same pattern, but rather were unchanged from the rest condition to the 20 Hz stimulus frequency (Fig. 5).

In the regions of interest analysis, compared with the rest condition, the 4 Hz stimulus elicited a significant increase of rCBF in the postcentral gyrus (areas 1 and 2) and in the cortex on the posterior bank of the rolandic sulcus (area 3b) (Table 2). In the precentral gyrus, however, the increase of rCBF was not significant. Further, in the rest condition, there was no difference in the rCBF increase between the motor cortex (area 4) and parietal cortex (areas 1 and 2), but at the 4 Hz stimulus frequency, the difference was significant

Table 1 *Areas of significant rCBF changes during median nerve stimulation*

Region	Frequency (Hz)	Talairach coordinates			Adjusted rCBF (ml/dl/min)		Increase in rCBF (%)	Z score
		x	*y*	*z*	Rest	Stimulation		
All subjects (n = 10)								
S I	2	–38	–26	44	59.50	61.60	3.53	4.31
	4	–36	–24	44	59.60	63.00	5.70	6.16
Subgroup (n = 6)								
S I	2	–38	–24	48	56.50	59.50	5.31	3.45
	4	–38	–22	44	57.20	61.20	6.99	4.72
	8	–38	–22	44	58.80	61.90	5.27	3.86
	10	–40	–20	48	53.80	57.00	5.95	3.96
	12	–40	–22	44	57.60	60.70	5.38	3.71
	16	–38	–24	52	51.10	54.50	6.65	3.63
	20	–42	–20	44	55.00	58.10	5.64	3.70
S II	20	–48	–22	16	67.60	71.10	5.18	3.85

(Table 2). These results are illustrated in the PET individual subtraction images, where a cluster of activity is detected in the parietal areas but not in the crown of the precentral gyrus (Fig. 6).

Somatosensory evoked potential recordings

The amplitudes of the SEPs elicited by the various stimulus frequencies are summarized in Table 3. Amplitudes of the SEP components were reduced when the stimulus rate was increased. The Friedman nonparametric test showed a significant frequency effect ($P < 0.002$). The N135 potential showed a strong decrease in amplitude and at 4 Hz was not measurable in any of the subjects. For this reason, this potential was not included in the Friedman test analysis. Compared with the 0.2 Hz stimulus frequency, the 2 and 4 Hz frequencies elicited a significant reduction in the amplitude of all the components studied (Table 3).

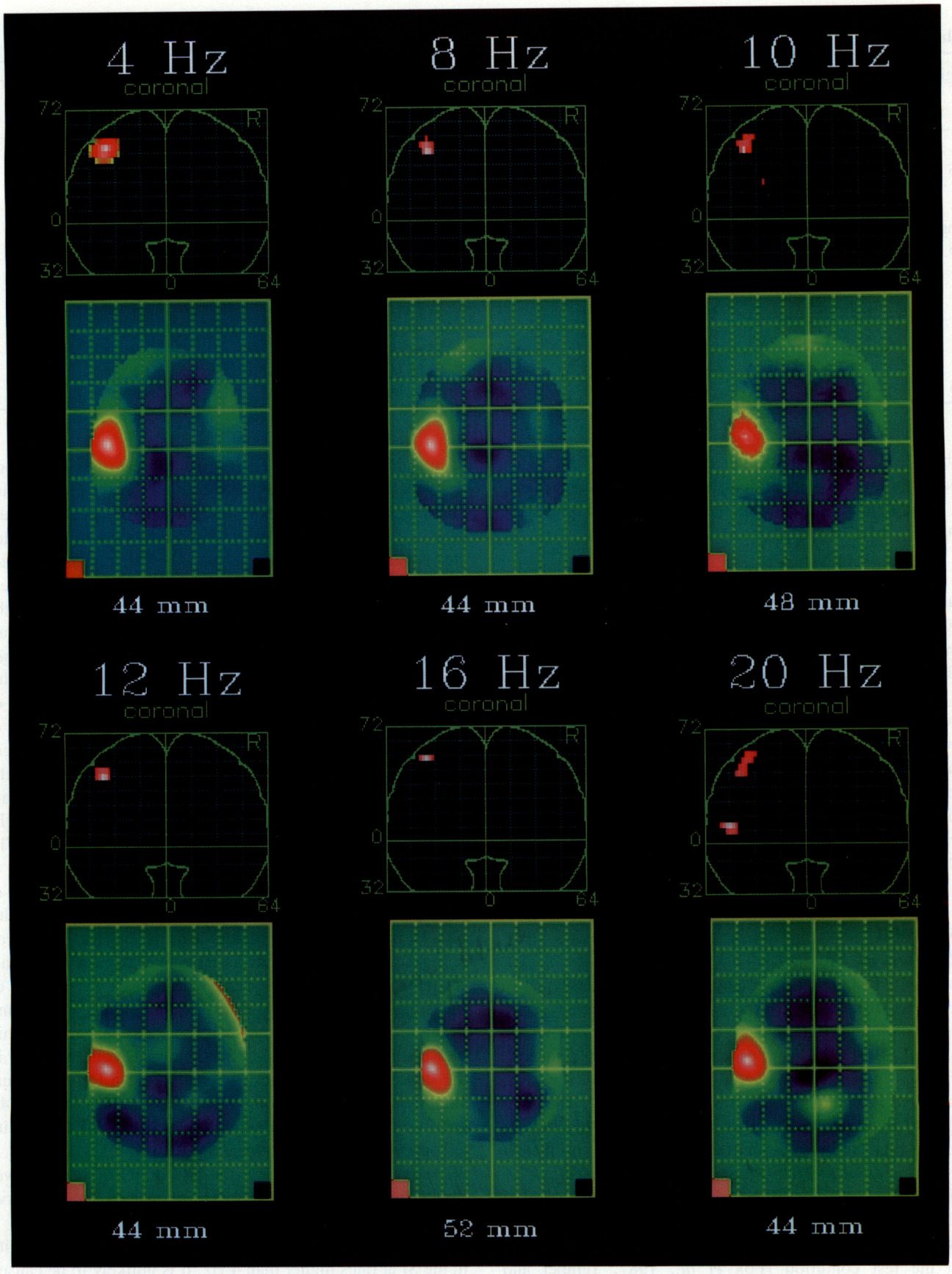
Discussion

Activation of SI

Previous PET studies of somatosensory cortex activation in humans used either a discrimination task requiring active motor exploration of the object (Ginsberg *et al.*, 1987, 1988; Seitz *et al.*, 1991) or a more passive task involving cutaneous vibratory stimulation (Fox *et al.*, 1987; Seitz *et al.*, 1991; Tempel and Perlmutter, 1992; Burton *et al.*, 1993). The latter method of stimulation is known from experiments in monkeys to elicit high frequency neuronal firing rates in the SI (Hyvärinen *et al.*, 1968; Mountcastle *et al.*, 1969). PET studies performed in humans during vibratory stimulation of the hand at high stimulus rates, usually higher than 100 Hz, showed a significant increase of rCBF in the SI compared with the rest condition (Fox *et al.*, 1987; Tempel and Perlmutter, 1992).

In the present study, we used electrical square-wave pulses identical to those used to elicit SEPs in order to study cerebral activation, as well as rCBF changes, with increasing stimulus frequency. For almost all of the stimulus frequencies, there was a significant increase of rCBF restricted to the cortex just posterior to the central sulcus. The Talairach coordinates of the most significant pixel at the 4 Hz stimulus rate, where the highest increment of rCBF occurred, correspond to the SI and particularly the posterior wall of the central sulcus, which is denominated area 3b in monkeys (for review, *see* Kaas, 1983). Only the scans performed at the slowest stimulus rates (0.2 and 1 Hz) did not show any significant increase of activity in the SI. The absence of a significant increase of activity at the slowest frequencies is probably due to delivery of insufficient stimuli during the scan (Fox and Raichle, 1984). At stimulus rates higher than 1 Hz, the significant activation of the SI was a constant finding, although the increase of rCBF varied for each stimulus frequency. The rCBF in the SI increased linearly from the rest condition to the 4 Hz stimulus frequency and then reached a plateau or even declined. The increase in rCBF with increased stimulus rate is not surprising because activity on the PET scan corresponds to the integrated counts over the scanning time. An increase in the stimulus rate will increase the number of times the neuronal activity is evoked in a particular area, and hence the rCBF, during the scan time. A linear relationship between rCBF and stimulus frequency has been reported in the striate cortex with rates of up to 7.8–15.5 Hz with visual stimulation by light-emitting diodes (Fox and Raichle, 1984), and in primary motor cortex with rates of up to 2–4 Hz with an opponent index movement (Sadato *et al.*, 1994). It is unclear which factors cause the rise of rCBF in the lower frequency range, but the spike frequency in the nerve terminals induced by the stimuli could be one of them.

It is more difficult to explain the saturation of the activity in the SI at rates higher than 4 Hz. It is unlikely to be caused by maximal neuronal firing in somatosensory cortex. Indeed, electrophysiological studies of somatosensory cortex in


4 Hz
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monkeys have shown that some neurons in parietal cortex areas 3 and 1 can be rhythmically entrained by a peripheral mechanical stimulus of up to 40 Hz, whereas others can increase their rate of discharge in response to high frequency peripheral stimuli (Hyvärinen *et al.*, 1968). Thus, a limitation of rCBF is more likely responsible for this saturation (i.e. a maximum increase of rCBF is reached at a given frequency in a particular cortical area). The results suggest that loss of the linear relationship between neuronal firing and rCBF occurs when a critical neuronal firing rate in a given cortical structure is reached. The PET studies using a continuous vibratory stimulus at higher frequencies than those we used (Fox *et al.*, 1987; Tempel and Perlmutter, 1992) agree with this hypothesis; their mean rCBF increase of ~20% is similar to the increase we obtained with the regions of interest analysis at the 4 Hz stimulus rate (Table 2).

Our findings on the effects of the stimulus frequency on SEP amplitudes are similar to those of other studies (Pratt *et al.*, 1980; Abbruzzese *et al.*, 1990*b*; Delberghe *et al.*, 1990; García-Larrea *et al.*, 1992). It is clear that there is an uncoupling between excitatory neuronal firing and increase of rCBF. The amplitude of the potential field recorded on the scalp is related to the number of cortical neurons excited by the stimulus. At stimulus frequencies of 0.2–4 Hz, the SEP amplitudes of the different components decreased progressively, whereas the rCBF increased in a linear fashion. The amplitude attenuation of the SEP components elicited at high stimulus frequencies cannot be related to the refractory period of the neuronal population because the interval between stimuli (250 ms at 4 Hz) is too long. The amplitude decrease of the SEP components is probably caused by complex inhibitory mechanisms mediated by GABAergic connections within the parietal cortex (for review, *see* Whitsel *et al.*, 1991) that reduce the excitatory postsynaptic potentials on those cells that generate the SEP components. It is likely then that the increase of rCBF could persist, whereas neuronal inhibition leading to a reduction in SEP amplitude could intensify. Another concomitant cause that can account for the reduction in the amplitude of SEPs is that the neurotransmittor release at presynaptic terminals would fail to follow a critical frequency, therefore decreasing the number of postsynaptic potentials. However, this latter mechanism cannot, by itself, account for the persistence of the rCBF increase.

The area activated at the 4 Hz frequency seemed larger than the area activated at the higher stimulus rates. However, the statistical methodology used in this study, which included Gaussian smoothing of the data, does not allow any definite conclusion about the effect of the stimulus frequency on the extent of the area activated, but it could be explained by a larger increase of rCBF. Further studies of this observation are called for, as animal studies show evidence that in the parietal cortex structures there is short-term plasticity with reduction of the activity volume after exposure to a repetitive tactile stimulus (Whitsel *et al.*, 1989, 1991; Lee and Whitsel, 1992).

With the exception of the 20 Hz stimulus rate, the SI was the only area activated in our somatosensory stimulation paradigm in which no special attention to the stimulus was required. The area within the sylvian fissure of the contralateral hemisphere activated by the 20 Hz stimulus rate

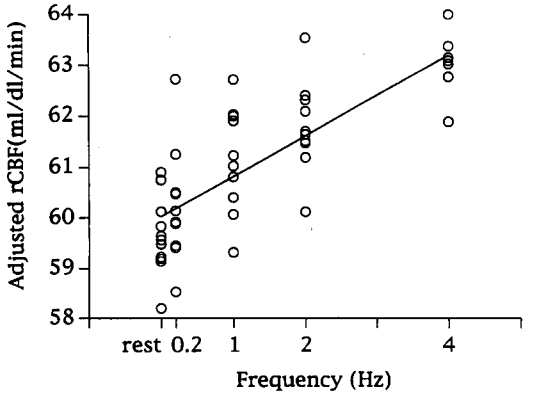

Fig. 3 Values for adjusted rCBF in SI for rest and stimulus conditions at the coordinates with highest Z value at 4 Hz (–36, –24, 44) in the 10 subjects. A linear relationship is clearly illustrated. The equation of the best fit straight line is: $y = 0.8x+60$, $r = 0.8$.

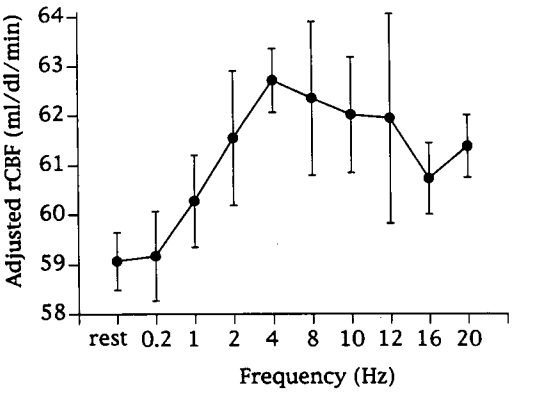

Fig. 4 Values for adjusted rCBF in SI for rest and stimulus conditions at the coordinates with highest Z value at 4 Hz (–38, –22, 44) in the subgroup of six subjects. A maximum rCBF increase occurs at the 4 Hz stimulus rate and then saturates or decreases progressively.

Fig. 2 $SPM_{\{t\}}$ values and orthogonal projections of the significant Z values for the 4–20 Hz stimulus rates show activation of the primary somatosensory area SI. At the 20 Hz stimulus rate, a second area is highlighted above the sylvian fissure and could correspond to the somatosensory area SII. The extent of the area activated is higher for the 4 Hz stimulus rate, where the increase of cerebral blood flow reached the maximum.

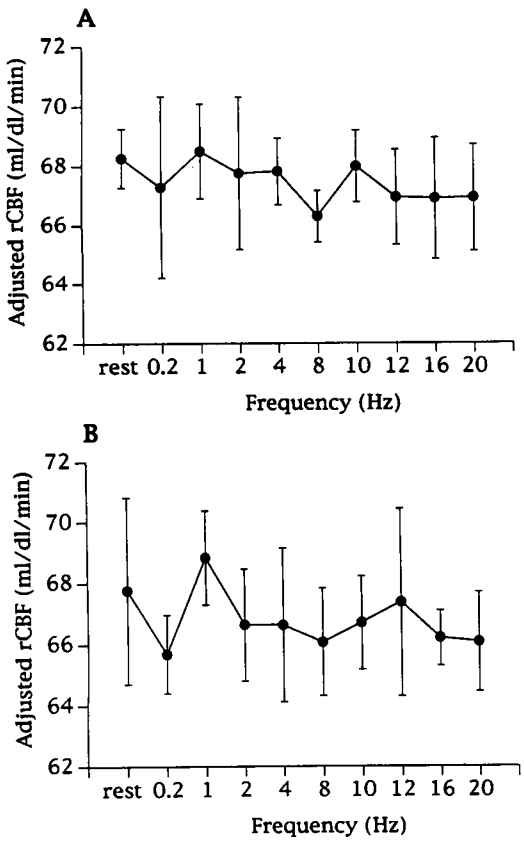

Fig. 5 Values for adjusted rCBF in (**A**) anterior (coordinates –4, 10, 56) and (**B**) posterior (coordinates –4, –10, 56) SMA. Increasing the stimulus frequency had no effect on rCBF.

corresponded in location to the secondary somatosensory area (SII) (Penfield and Jasper, 1954). The reason for activation of this area only at the highest stimulus frequency remains unclear. In humans, information about the localization and functional activity of this area is sparse. A PET study (Burton *et al.*, 1993) using vibratory stimuli applied to the hand at 130 Hz showed a zone of significant rCBF changes whose localization is closely similar to ours. This study, in which a method for detection of individual activation clusters and *t* statistics were used, also showed activation of the posterior insula. In our study, subtraction images between the 20 Hz stimulus frequency and the rest condition co-registered to MRI showed clusters of activation in the upper wall of the sylvian fissure and in the posterior insula; the localization of these clusters was variable between subjects. The image smoothing procedure used in SPM analysis smeared the activity of this region and detected a maxima of significant changes. The poor reproducibility of the SII activation is also in agreement with the electrophysiologial studies performed during surgical intervention, where evoked potentials were not detected constantly in humans after peripheral stimulation (Lüders *et al.*, 1985; Allison *et al.*, 1989).

Table 2 *Normalized rCBF values in motor and parietal cortices*

Cortical area	Normalized rCBF		
	Rest	4 Hz	*P* value
Motor cortex			
Area 4	51.51±2.65	53.16±3.63	NS
Parietal cortex			
Areas 1 and 2	52.48±5.08	60.33±7.97	<0.002
Area 3b (lateral)	54.09±6.55	60.90±7.13	<0.01
Area 3b (medial)	52.05±7.95	56.76±5.68	<0.04

Values are mean±SD.

Absence of activation of motor areas during median nerve stimulation

Cortical areas involved in motor processing, such as the SMA and the premotor and motor cortices, that are activated in PET studies during different motor paradigms (Colebatch *et al.*, 1991; Deiber *et al.*, 1991; Grafton *et al.*, 1993) did not show any significant increase of rCBF, even at a stimulus rate of 4 Hz when the SI activation reached its peak.

In the SMA, particularly, there was no linear relationship between the rCBF and the stimulus rate in the range of up to 4 Hz in contrast with the correlation found in the somatosensory cortex. The absence of activation was found not only in the anterior part of the SMA, which is thought to be involved in the selection of movement (Deiber *et al.*, 1991; Passingham, 1993), but also in the posterior SMA, which receives input from striatal structures and parietal area 5 and in turn sends projections to the primary motor cortex (Passingham, 1993). Our finding of the absence of SMA activation during median nerve stimulation disagrees with the results of a ^{133}Xenon study (Foit *et al.*, 1980) that showed a significant increase of SMA activation with median nerve stimulation in two out of seven subjects. The reason for this divergence can be found in the study's smaller threshold level of significance. Although the coordinates of the localization of SMA were not reported, some studies using vibratory stimulation describe the activation of this area (Fox *et al.*, 1987; Tempel and Perlmutter, 1992). The results of these studies cannot be compared with ours because cutaneous vibratory stimuli are known to produce a tonic finger flexion reflex (Torebjörk *et al.*, 1978), as well as a transient severe hypoaesthesia for vibration, joint position sense, and kinaesthesia (Ibáñez *et al.*, 1989; Macefield and Burke, 1991), whose mechanisms at a central level are not fully understood.

Thus, the results of our study suggest that the SMA is unlikely to be a primary contributor to the generation of SEPs elicited by conventional methods and therefore responsible for a SEP component such as N30. This conclusion raises the question of whether the changes in N30 associated with diseases involving the basal ganglia are due to SMA dysfunction (Rossini *et al.*, 1989, 1993; Abbruzzese *et al.*, 1990*a*; Reilly *et al.*, 1992; Töpper *et al.*, 1993).

Another issue is whether the part of the motor cortex

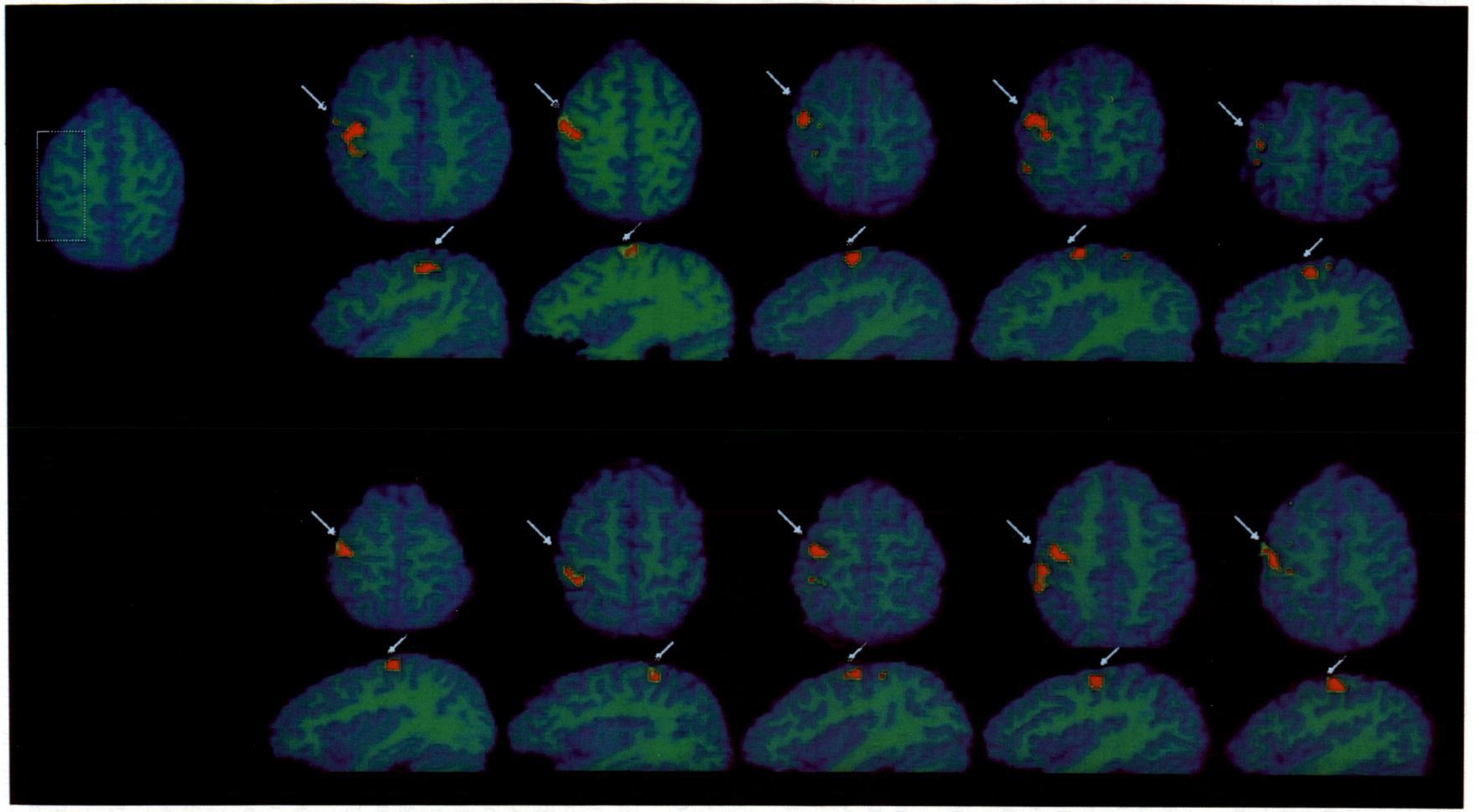

Fig. 6 Superimposed transverse and sagittal MRI and PET images of the 10 subjects. To represent the results obtained by regions of interest analysis, a Gaussian kernel filter of 5×5 pixels was computed to the PET images and a subtraction between scans at the 4 Hz stimulus rate and the rest condition was obtained. Only rCBF above 46 ml/dl/min (2 SD below the mean calculated for motor cortex at rest in Table 2) was computed and the threshold set to 10% (mean percentage of the rCBF increase calculated on the area 3b) of the maximal pixel value obtained in the subtraction. The PET image subtraction was edited to leave only the region inside of the rectangle in the five planes used for regions of interest calculations. The images show a well-defined cluster of activity on the posterior bank of the central sulcus in most subjects, but no consistent cluster of activity on the crown of the precentral gyrus (arrows).

Table 3 *Effects of stimulus rate on SEP amplitude*

SEP component	0.2 Hz	1 Hz	2 Hz	4 Hz	*P* value
N20	2.13±0.90	1.87±0.95	1.35±0.43	1.11±0.50	<0.006†
N30	3.51±2.83	2.55±2.35	1.53±0.96	0.89±0.43	<0.006*†
P45	4.32±1.93	3.08±1.15	1.95±0.53	1.90±1.37	<0.006†
N70	4.11±3.14	2.04±1.76	1.40±1.32	1.49±1.05	<0.006*†
N135	3.57±3.75	0.86±0.41	0.67±0.21	–	

Values are mean±SD SEP amplitudes. *For the comparison between 0.2 and 2 Hz; †for the comparison between 0.2 and 4 Hz.

situated on the crown of the precentral gyrus, which is thought to be the generator of P22, is activated by peripheral nerve stimulation. The SPM methodology using stereotaxic normalization of brain and Gaussian filtering of the pixel values increases the signal-to-noise ratio but also corrects for the intersubject anatomical variation of the gyri, which can cause spreading of data and blurring of the outer limits of the area activated. The region of interest analysis can overcome this problem when the structure to be measured is easily identifiable. In the part of the motor cortex situated on the crown of the precentral gyrus, we found no difference in rCBF between the rest condition and the 4 Hz stimulus and no relationship between the rCBF and the stimulus frequency. Therefore, this structure is unlikely to be the generator of the P22 component.

rCBF increases and SEP generators: the problem of dissociation between parietal and frontal structures

If the generators for scalp-recorded parietal and frontal components were separate, only two components, P22 and N30, would be generated in the motor areas. A finger-dependent somatotopic representation for the P22 component has been found over the central areas (Deiber *et al.*, 1986), and because of its radial orientation (Desmedt and Bourguet, 1985) its generator would have to be situated in the neurons of the motor cortex close to the surface (Mauguière *et al.*, 1983; Desmedt and Bourguet, 1985). On the other hand, the N30 potential distributes largely on the frontal regions of both hemispheres, and may be generated in the SMA (Desmedt and Bourget, 1985; Rossini *et al.*, 1989).

These hypotheses about the generators of P22 and N30 are not supported by the results of the present study, where the increase of activity following stimulation of the median nerve was limited to the somatosensory areas 3b, 1 and 2. This finding supports the hypothesis advanced by Allison *et al.* (1991, 1992), which posits that the early SEP components are generated exclusively in SI. Discussion of the radial or tangential nature of each SEP generator is beyond the scope of this paper, but spatio-temporal dipole modelling shows that P22, if a genuine component, would be a radial dipole in the contralateral hand area (Franssen *et al.*, 1992).

The strongest point favouring the existence of motor cortex structures as generators of the 'frontal components' is the selective losses of parietal or frontal components in patients with cortical lesions (Mauguière *et al.*, 1983; Yamada *et al.*, 1984; Slimp *et al.*, 1986; Mauguière and Ibáñez, 1990).

An explanation for the discrepancy between clinical neurophysiological and metabolic data can be advanced from animal and human studies. Indeed, in monkeys the parietal cortex area SI is organized in a series of pericolumnar functional interactions in which columns receiving excitatory inputs of a receptive field inhibit the adjacent columns (Juliano *et al.*, 1989; Whitsel *et al.*, 1991; Lee and Whitsel 1992; Lee *et al.*, 1992). The organization of these functional columns can be modified by tactile stimuli (short-term plasticity). On the other hand, in humans the cortical SEP components, and mainly the frontal N30, are very sensitive to the effect of interferences like vibration (Jones, 1981), movement (Cohen and Starr, 1987) and mental movement (Cheron and Borenstein, 1992). The last task is known to activate both motor and parietal cortex in the absence of actual movement (Hallett *et al.*, 1994). Therefore, it can be hypothesized that a functional modification of some, but not all, of the SEP generators could happen *in situ* when a lesion, wherever its location, disconnects anatomical structures and changes the dynamics of the columnar organization within the parietal cortex. Thus, the nature of the dissociation between frontal and parietal SEP components observed in patients would be functional rather than anatomical. In agreement with this hypothesis are the findings that some frontal lesions cannot only decrease but also enhance (Mauguière *et al.*, 1987; Yamaguchi and Knight, 1990) the amplitude of the SEP components.

Although the results of the present study strongly support the hypothesis that the SEP components are generated exclusively in the parietal cortex, they do not answer the question of whether there is activation of the motor cortex adjacent to the central sulcus. Given the spatial resolution of the PET technique, some minimal activation of anatomical regions lying on the anterior bank of the central sulcus cannot be definitely separated from the SI activity in the posterior part of this sulcus. However, the Talairach coordinates of the maxima for each stimulus frequency correspond to an inferior plane and are more lateral than those described by Colebatch *et al.* (1991), where the subjects were performing distal and proximal movements. Furthermore, the subtracted images between the 4 Hz stimulus and the rest condition (Fig. 6) would be against such activation because the cluster of

activity does not appear to be centred on the central sulcus but a little behind it in most of the subjects. Studies with functional MRI can help to solve this problem because of its better spatial resolution and better assessment of dynamic changes.

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