Frequency Dependence of the Functional MRI Response After Electrical Median Nerve Stimulation

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Abstract: Localizing sensorimotor areas with high resolution functional MRI is of considerable interest for a wide range of medical applications from the preoperative planning of neurosurgical interventions to determining the course of neuroplastic reorganisation after brain lesions. We examined the effect of the stimulation frequency on the blood oxygen level dependent (BOLD) fMRI response and on perfusion weighted fMRI using electrical median nerve stimulation at 5, 15, 40, and 100 Hz. BOLD fMRI was performed using a single shot gradient echo EPI sequence to acquire 15 contiguous slices. For the qualitative flow sensitive studies, a single slice inversion recovery prepared spin echo echoplanar sequence (IR-SE EPI) was used. In the primary sensorimotor cortex, a linear increase of the fMRI-BOLD response, affecting both the number of activated pixels and the amplitude of the signal changes, was seen with increasing stimulation frequencies. The qualitative in-flow sensitive studies, using the IR-SE EPI sequence, indicate that the tissue perfusion also increases over the same range of frequencies. This implicates that larger fMRI responses can be obtained if electrical median nerve stimulation is performed at higher frequencies. The results are compared with electrophysiological data, which show a decrease of the early somatosensory evoked potentials at higher frequencies. *Hum. Brain Mapping* 9:106–114, 2000.

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INTRODUCTION

Functional magnetic resonance imaging (fMRI), using the blood oxygen level dependent (BOLD) signal changes [Ogawa et al., 1990], has become a widespread method for mapping cortical activation. One of the first fMRI studies demonstrated activation of the sensorimotor cortex in response to motor tasks [Ban-

dettini, 1992]. Since then, many groups have studied the response to motor tasks in greater detail [Rao et al., 1995; Schlaug et al., 1996; Sadato et al., 1997] and have shown the usefulness of fMRI for identifying the sensorimotor cortex prior to neurosurgical interventions [Atlas et al., 1996; Righini et al., 1996]. Good patient participation is required for these investigations, since activation task performance has been shown to influence fMRI activation strength [Baudendistel et al., 1996]. In severely compromised patients, motor tasks may not be applicable and the introduction of a passive stimulus would be helpful in these cases. Hammeke et al. [1994] have shown somatosensory cortex activation after tactile stimulation of the palm. Puce et al. [1995] investigated a variety of sensory stimuli

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(electrical stimulation of the median nerve, brushing of the thenar, pulsed flow of compressed air). Electrical median nerve stimulation, a well-established clinical stimulus for somatosensory evoked potentials (SEP), yielded inconsistent results in their setting, but recent reports have demonstrated sensorimotor cortex activation after direct median nerve stimulation [Davis et al., 1995, Baudewig et al., 1997; Büchert et al., 1997] and after electrical stimulation of individual fingers with ring electrodes [Kurth et al., 1997].

A clear frequency dependence of the fMRI response has been shown for finger movement rates, with a linear increase of the BOLD signal in the sensorimotor cortex with increasing movement frequencies from 1–5 Hz [Rao et al., 1996; Schlaug et al., 1996]. Positron emission tomography (PET) studies demonstrated that this increase in BOLD signal is correlated with an increase in regional cerebral blood flow (rCBF) [Ramsey et al., 1996; Sadato et al., 1997]. The frequency dependence of sensory stimulation has not been thoroughly investigated in humans to date. Data from anaesthetized animals [Gyngell et al., 1996] showed a decrease of the fMRI response measured at 4.7T for stimulation frequencies above 3 Hz, with negligible responses at 9 Hz. Based on the observation that the amplitude of the SEP declines above 5–8 Hz [Pratt et al., 1980; Delberghe et al., 1990], most previous fMRI studies using electrical nerve stimulation have not exceeded a stimulation rate of 10 Hz.

As discussed by Jueptner and Weiller [1995], the measurement of rCBF most likely represents synaptic activity independent of the excitatory or inhibitory character of the synapse. According to this hypothesis, the observed decline of the SEP amplitude above 7 Hz may not necessarily be paralleled by a reduction of the hemodynamic response and may in fact be followed by an increase in rCBF, leading to a stronger BOLD response at higher frequencies. The aim of the present study was to test this hypothesis and characterize the BOLD response and tissue perfusion after electrical median nerve stimulation in the range of 5 to 100 Hz.

MATERIALS AND METHODS

Nine healthy volunteers between the ages of 22 and 35 years served as subjects: 8 males, 1 female; all right handed, dexterity index = 0.74 according to Oldfield [1971]. Subjects were paid and gave written informed consent according to institutional guidelines.

Scans

Scans were obtained, using a clinical 1.5 Tesla scanner equipped with a standard quadrature head coil

and a high speed gradient set (SIGNA ECHOSPEED running version 5.6 of the General Electric software, Milwaukee, WI). BOLD fMRI was performed using a single shot gradient echo echoplanar sequence (EPI-BOLD) to acquire 15 contiguous 5-mm-thick axial slices, covering the primary and secondary sensory and motor areas in an interleaved manner. The sequence parameters were FOV = 20 x 20 cm, matrix = 64 x 64, nominal voxel dimensions = 3.1 x 3.1 x 5 mm, TR = 3 sec, TE = 60 msec, flip angle = 90°, sampling bandwidth = 125 kHz.

For the in-flow sensitive studies, a single slice inversion recovery prepared spin echo echoplanar sequence (IR-SE EPI) with the following parameters was used: FOV = 28 x 21 cm, acquired matrix = 96 x 72, with 8 of the phase encoding steps being acquired prior to the center of the spin echo at TE = 28 msec, TI = 1 sec, and TR = 3.5 sec. The slice thickness for the imaging sequence was 5 mm, while the inversion pulse was applied to an 8-mm-thick slice to ensure complete inversion of the spins in the imaging slice. The slice for the IR-SE EPI scan was positioned at the level of highest activation in the primary sensorimotor cortex, as determined with the EPI-BOLD sequence, and had a nominal resolution of 2.9 x 2.9 x 5 mm. A total 74 (EPI-BOLD) or 73 (IR-SE EPI) images were collected per slice, with the initial four (EPI-BOLD) or three (IR-SE EPI) images being discarded to avoid non-steady state effects.

Procedures

Before entering the scanner, each subject was informed about the procedure, and the threshold stimulation intensity for a motor response was determined. Electrical stimulation of the median nerve was obtained by applying 0.2 ms pulses to the left wrist. The necessary current for reaching the motor threshold varied between subjects (range 5.1–13 mA), but was rather independent of the stimulation frequency for a given subject. The frequencies used for the fMRI studies were 5, 15, 40, and 100 Hz, with a stimulation intensity slightly above motor threshold. The intensity was held constant for all stimulation frequencies. The volunteers were instructed to keep their eyes closed during the scanning procedure. The stimulation paradigm always began with a control period with no stimulation, which was followed by alternating periods of stimulation and rest with a total of three activation and four rest periods. The period length was 30s for EPI-BOLD and 35s for IR-SE EPI. The order of the EPI-BOLD series for the four frequencies (5, 15, 40, and 100 Hz) was pseudo-randomized between sub-

jects. After preliminary analysis of the EPI-BOLD data, the single slice for the IR-SE EPI studies was selected at the anatomical position showing highest activation in the primary sensorimotor cortex. The stimulation protocol for the IR-SE EPI series was the same as for the EPI-BOLD scans.

Data analysis

The standard General Electric software is restricted to a total of 512 images per series due to a software limitation imposed by the database manager. This limits the number of slices that can be acquired while retaining a sufficient number of images per slice for a robust detection of functional activation. To overcome this limitation, a modified version of the pulse sequence was provided by GE, in which the raw data for the series is written directly to disk with no reconstruction on the SIGNA, thus avoiding the limitation imposed by the database manager. At the end of each series, the EPI-BOLD data were transferred to a workstation, where off-line reconstruction of the data was performed using a program provided by the University of Wisconsin. For the single slice IR-SE EPI scan, the 512 image limit did not represent a problem and data were reconstructed on the scanner using the standard GE software. Data reconstruction applied a Fermi filter with a width of 10 and a radius of 32 (EPI-BOLD), or 48 (IR-SE EPI) pixels. After reconstruction, the EPI-BOLD data were motion corrected using the 3D rigid body algorithm in the public domain AIR program [Woods, 1992]. For the IR-SE EPI images, an in-plane motion correction was performed using the motion correction algorithm included in the public domain AFNI software from the Medical College of Wisconsin [Cox, 1997]. Following the motion correction, activation maps were derived using a cross-correlation function [Bandettini, 1993]. The cross-correlation maps were subsequently processed using a neighborhood criterion, which required that at least 6 out of 25 pixels in a 5×5 region centered on the current pixel were also active. This limits us to observing relatively large areas of activation, but increases the robustness of the detection (i.e., decreases the P value) [Forman, 1995]. The threshold of the cross-correlation function was 0.5 for the EPI-BOLD studies (corresponding to a nominal P value of 2.9×10^{-5}) and 0.3 for the IR-SE EPI series (corresponding to a nominal P value of 0.01). Time intensity curves for the sensorimotor cortex were derived, by averaging the response from all activated pixels within a box of 4×4 cm, centered on the area representing the motor hand area [Yousry, 1997]. For each region of interest

(ROI), the number of activated pixels and the average time intensity profiles of activated pixels were calculated. Linear trends were subtracted from the time intensity curves, using the first 10 and the last 5 images for baseline calculation. The amplitude of activation was calculated as percent change compared to the baseline signal intensity. To account for the hemodynamic delay, the first two images in each stimulus interval were discarded when calculating the signal changes.

Since no activation was observed at any stimulation frequency for the volunteer who fell asleep during the experiment, statistical analysis was performed only on the eight remaining subjects. To allow a better comparison between the two sequences, the number of activated pixels and the amplitude of the signal changes for the EPI-BOLD sequence were determined both for a single slice, which was at the same level as the perfusion sensitive sequence, and for all slices.

Differences in the number of activated pixels and in the amplitude of the signal, due to the stimulation frequency, were tested for significance by a two-factorial multivariate analysis of variance (MANOVA) for both EPI-BOLD vs IR-SE EPI and for the four frequencies (5, 15, 40, and 100 Hz). Where a significant effect was found, univariate F-Tests were performed to identify the variable(s) (number of pixels and/or signal change) that contributed significantly to these effects. For locating the frequency pairs with significant differences in the number of pixels or in the amplitude of the signal change, tests with contrast were carried out. As nominal level of significance $\alpha \leq 0.05$ was accepted and corrected (Bonferroni adjustment) for all posthoc tests (F-tests and tests with contrasts) in order to keep the type I error less or equal to 0.05. For identifying the best curve fit, a trend analysis was performed using polynomial contrasts in MANOVA.

RESULTS

With the BOLD sensitive EPI sequence, a regular activation of the primary sensorimotor cortex (S1) was seen after electrical median nerve stimulation. The electrically evoked sensation was perceived as small pricks at lower stimulation frequencies and as a non-painful tingling sensation at higher frequencies. Seven of the eight awake individuals showed a response at 5 Hz stimulation frequency, six at 15 Hz and all eight at 40 and 100 Hz. One of the volunteers fell asleep during the experiment. In this candidate no activation was observed at any stimulation frequency. Functional maps obtained from one individual during electrical median nerve stimulation at 5, 15, 40, and 100 Hz

Figure 1.

Typical activation maps from one subject obtained in response to stimulation at 5, 15, 40, and 100 Hz. **(a)** Coronal and transaxial representations of the activation maps obtained with the multiple slice EPI-BOLD sequence. In the color scale, cross-correlation values of 0.5–1.0 are represented by a transition from red to yellow, while cross-correlation values from -0.5 to -1.0 are represented by a transition from dark blue to light blue.

(b) Activation maps obtained with the single slice perfusion sensitive IR-SE EPI sequence. Cross-correlation values of 0.3–1.0 are represented by a transition from red to yellow, and cross-correlation values from -0.3 to -1.0 are represented by a transition from dark blue to light blue.

stimulation frequency and 6.9 mA stimulus intensity are shown in Figure 1. The number of activated pixels shows a clear frequency dependence. The activation of the primary sensorimotor cortex (S1) could be followed over several slices. The total number of activated pixels in the primary sensorimotor cortex of all subjects was pooled and the results are presented in Figure 2a. Signal changes were in the range of 1.2–3.0%. The best fit to the number of active pixels was a linear fit ($P = 0.003$), with a slope of 16.0 pixels/10 Hz and an intercept value of 59 pixels. Figure 3a shows the mean time intensity profiles at 5, 15, 40, and 100 Hz. A frequency dependence can also be observed here (Fig. 4a). The best fit to the rise in amplitude was a linear fit ($P = 0.012$), with a slope of 0.08%/10 Hz and an intercept value of 1.86%.

For the in-flow sensitive IR-SE EPI sequence, a response was observed in 2, 5, 6, and 7 out of eight subjects (at 5, 15, 40, and 100 Hz, respectively). Figure 1b shows the perfusion weighted activation maps of the same subject as in Figure 1a. The number of activated pixels paralleled the frequency dependence observed in the BOLD experiments (Fig. 2b). As with the BOLD data, the increase of the number of active pixels was best represented by a linear curve ($P = 0.011$), with a slope of 1.4 pixels/10 Hz and an intercept value of 2.5 pixels. The mean time intensity curves are shown in Figure 3b. The amplitudes varied between 1.9–4.4% and showed a trend to higher values with higher stimulation frequencies (slope 0.08% /10 Hz; intercept value of 2.69%). Correlation maps indicate a linear association between the BOLD response and the

in-flow response over the investigated frequency range ($r = 0.68$; $P < 0.001$). Although not thoroughly investigated in this study, the BOLD experiments also showed activation outside the contralateral primary sensorimotor region (S1), with 7 of 8 volunteers showing activation in the contralateral SII and 5 of 8 showing activation in the ipsilateral SII region. Only occasionally activation was seen in the ipsilateral S1 region (2 of 8), SMA, or thalamus (one each). Activation in all these regions was considerably lower than in the contralateral S1 region, on which this study focused, and usually only included a few pixels (6–20).

DISCUSSION

Localizing sensorimotor areas with high resolution functional MRI is of considerable interest for a wide range of medical applications, from the preoperative planning of neurosurgical interventions to determining the course of neuroplastic reorganisation after brain lesions. Simple motor tasks, such as finger tapping, which are well established for functional cortical activation, have the disadvantage of being performance dependent. To overcome this difficulty, sensory stimuli may be helpful. Electrical median nerve stimulation, a well-established clinical stimulus for somatosensory evoked potentials (SEP), represents a method for overcoming this problem. We investigated the effect of the stimulation frequency on the fMRI-BOLD response and on tissue perfusion.

Factors contributing to the amplitude of the BOLD response include local blood volume changes and changes in the concentration of deoxyhemoglobin (HbR) within the vessels. The relative timing and contributions of the changes in the blood volume, blood flow, and tissue oxygen consumption to the observed BOLD effect is still a subject of debate [Malonek et al., 1997; Rosen et al., 1998]; however, it is accepted that the main component of the BOLD response (an increase in signal) represents the net effect of contributions from all three parameters on the local concentration of HbR. Since the exact nature of the coupling of brain activity, cerebral blood flow, and BOLD response is still not completely understood, we also implemented a perfusion-sensitive sequence in addition to the BOLD sensitive one. The IR-SE EPI sequence, used to provide the perfusion-sensitive data in this study [Kwong et al., 1992], has the disadvantage that it does not compensate for the BOLD effect (unlike the FAIR sequence) [Kim, 1995], which means that the signal changes cannot be interpreted purely in terms of perfusion changes and thus cannot be used to calculate the change in CBF during stimulation. How-

Figure 2.

Number of activated pixels in the primary sensorimotor cortex during electrical median nerve stimulation. (a) Data from the BOLD sensitive sequence, the white columns show the total number of activated pixels and the shaded columns show the number of activated pixels in a single slice, which was at the same level as the perfusion-sensitive experiment. (b) Data from the perfusion-sensitive IR-SE EPI sequence. Each bar graph entry contains the contribution of eight subjects for both sequences; subjects showing no response at a given frequency were considered to have 0 activated pixels. Error bars indicate the SEM and significant differences ($P < 0.05$) are indicated by a star (*).

ever, by using a spin echo sequence with a short echo time, we tried to minimize the BOLD contribution to the signal change, so that the data can be considered to be perfusion sensitive. The inversion interval of 1 sec should be long enough to minimize the intravascular contribution from arteries supplying the imaged plane (or from arteries that transect, but do not perfuse the slice) [Edelman et al., 1994]. Since close to full exchange of the labeled spins is expected to occur in the capillary bed, there should be little or no venous component to the observed signal change. The magnitude of the tissue perfusion, as determined with the IR-SE EPI sequence, follows the magnitude of the fMRI BOLD response linearly in the investigated range of 5–100 Hz stimulation frequency, suggesting that the BOLD changes in the microvasculature are directly paralleled by regional changes in CBF, presumably reflecting the degree of neuronal activity. A similar tight relationship, between regional CBF and BOLD changes at different stimulation frequencies, has recently been described by Zhu et al. [1998] in response to visual stimulation.

The only other report we know of that investigates regional cerebral blood flow after electrical median nerve stimulation is by Ibanez et al. [1995], who used ^{15}O -labeled water PET to measure rCBV and observed a steep increase in blood flow from 0.2–4 Hz (0.8% per Hz). Above 4 Hz, the response of the rCBF leveled off

Figure 3.

Mean time intensity profiles from activated pixels after electrical median nerve stimulation at 5, 15, 40, and 100 Hz stimulation frequency. (a) Data from the BOLD-sensitive sequence. (b) Data

from the perfusion-sensitive IR-SE EPI sequence. The bars beneath the time intensity curves indicate when the electrical stimulation was applied.

and even seemed to decrease at 20 Hz stimulation frequency. The range between 0.2–4 Hz was not investigated by us since preliminary investigations had yielded rather inconsistent BOLD responses with stimulation frequencies below 5 Hz. In contrast to Ibanez [1995], we observed a continuous increase of the amplitude with the BOLD-sensitive EPI sequence and a trend to higher amplitudes with the perfusion-sensitive IR-SE EPI sequence even above 16 Hz. In agreement with their data, the increase above 5 Hz observed by us is much less steep (0.008% per Hz), indicating that this effect might be of different origin. This is discussed below in connection with the electrophysiological literature. Of interest is the observation that the activated area, as determined with both sequences (the BOLD sequence and the perfusion-sensitive IR-SE EPI sequence), increases with the stimulation frequency. Ibanez et al. [1995] indicated that the area activated seemed larger at the higher stimulus rates, but the poor spatial resolution of PET and their statistical methodology, which included Gaussian smoothing of the data, did not allow any definite conclusion about the effect of the stimulation frequency on the extent of the area activated. The enlargement of the activated area might reflect an in-

crease in lateral inhibition with increasing stimulation frequency and an expansion of the receptive field in the primary somatosensory cortex [Florence et al., 1997].

The coupling of electrical activity and metabolism has been investigated in animal studies and showed that the glucose utilization in the dorsal horn of the spinal cord displayed a linear dependence with the frequency used for electrical stimulation of the sciatic nerve [Kadekaro et al., 1985]. Interestingly, the metabolic activity in the dorsal root ganglion cells did not increase in these experiments, indicating that glucose uptake is most likely related to synaptic activity and not to an enhanced metabolic activity of the corresponding cell bodies. Experiments, using the superior cervical ganglion as a model of the central nervous system, yielded a similar linear frequency dependence of electrical stimulation on glucose consumption [Yarowski et al., 1983 and 1985].

At first sight, the functional MRI data presented here contrast with electrophysiological data, which show a reduction of the somatosensory evoked potentials (SEP) at stimulation rates above 5–8 Hz [Pratt et al., 1980; Delberghe et al., 1990]. Of the primary cortical response to electrical median nerve stimulation,

Figure 4.

Mean amplitude of the signal changes in the time intensity curves. Error bars indicate SEM: (a) BOLD-sensitive sequence; 7, 6, 8, and 8 subjects contributed data to the bar graphs at 5, 15, 40, and 100 Hz, respectively; (b) perfusion-sensitive IR-SE EPI sequence; 2, 5, 6, and 7 subjects contributed data to the bar graphs at 5, 15, 40, and 100 Hz, respectively.

the N20 component is supposed to be generated in the primary somatosensory cortex by EPSPs (excitatory postsynaptic potentials) in pyramids of area 3b [Allison et al., 1991]. In addition to the primary SEP responses, high frequency potential oscillations around 600 Hz have been shown to concur with the N20 component [Eisen et al., 1984; Emori et al., 1991]. Hashimoto et al. [1996] have provided evidence that these high frequency components reflect activity of inhibitory neurons and proposed that these represent GABAergic inhibitory interneurons of layer 4 in area 3b. The reduction of the N20 component at higher frequencies can be explained by increased activity of these neurons, but this does not imply that energy metabolism is likewise reduced. Nudo and Masterton [1986] have demonstrated that activation of inhibitory and the activation of excitatory afferents increase glucose uptake. As discussed by Jueptner and Weiller [1995], energy consumption is independent of the excitatory or inhibitory nature of a synapse. Curio et al. [1994] have shown that the sources of the high frequency oscillations are co-localized with the generators of the N20 component. Being localized at the same site, they can clearly contribute to the fMRI response in the hand area of the primary somatosensory cortex.

If the activity of inhibitory interneurons contributes especially to the fMRI response at higher stimulation frequencies, then this can explain the discrepancy of our results with the observations of Gyngell et al. [1996], who saw a continuous decline of the fMRI response from 1.5–9 Hz after electrical stimulation of the forepaw in chloralose anaesthetized rats. In contrast to the N20 component of the SEP, which is rather resistant to state parameters such as waking and sleep [Lüders et al., 1986], or barbiturate-induced coma

[Hume et al., 1979], the high frequency oscillations superimposing the N20 component of the SEP show a strong state dependency and disappear during sleep [Emerson et al., 1988; Yamada et al., 1988; Hashimoto et al., 1996]. In humans, Antognini et al. [1997] have shown, that isoflurane anaesthesia blunts the fMRI response to noxious and innocuous stimuli. It is interesting to note that the only volunteer in which we did not observe a fMRI response at any stimulation frequency was the one who fell asleep during the experiment.

In summary, this study shows an increase in both the fMRI-BOLD response and the tissue perfusion after electrical median nerve stimulation in the range of 5–100 Hz. It is speculated that this increase most likely reflects inhibitory, rather than excitatory, synaptic activity and is of different origin than the steeper increase in tissue perfusion after electrical median nerve stimulation in the range of 1–4 Hz observed by Ibanez et al. [1995] in PET studies. Further electrophysiological studies are necessary to see if the inhibitory 600 Hz oscillations generated in the primary somatosensory cortex show a similar frequency dependence in the range of 5–100 Hz, which would strengthen the hypothesis presented here.

Some of the previous studies using an electrical stimulus for functional brain mapping have obtained rather inconsistent results. We believe that this is most likely due to a too low stimulation frequency (e.g., 2–10 Hz). As the presented results indicate, higher stimulation frequencies will most likely yield more robust fMRI responses. In a clinical setting we suggest using stimulation frequencies around 100 Hz for identifying the somatosensory cortex with fMRI.

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REFERENCES

- Allison T, McCarthy G, Wood CC, Jones SJ. 1991. Potentials evoked in human and monkey cerebral cortex by stimulation of the median nerve: a review of scalp and intracranial recordings. *Brain* 114:2465–503.
- Antognini JF, Buonocore MH, Disbrow EA, Carstens E. 1997. Isoflurane anesthesia blunts cerebral responses to noxious and innocuous stimuli: a fMRI study. *Life Sci* 61: 349–354.
- Atlas SW, Howard RS 2d, Maldjian J, Alsop D, Detre JA, Listerud J, D'Esposito M, Judy KD, Zager E, Stecker M. 1996. Functional magnetic resonance imaging of regional brain activity in patients

- with intracerebral gliomas: findings and implications for clinical management. *Neurosurgery* 38: 329–338.
- Bandettini PA, Wong EC, Hinks RS, Tifofsky RS, Hyde JS. 1992. Time course EPI of human brain function during task activation. *Magn Reson Med* 25:390–97.
- Bandettini PA, Jesmanowicz A, Wong EC, Hyde JS. 1993. Processing strategies for time-course data sets in functional MRI of the human brain. *Magn Reson Med* 30:161–173.
- Baudendistel K, Schad LR, Wenz F, Essig M, Schroder J, Jahn T, Knopp MV, Lorenz WJ. 1996. Monitoring of task performance during functional magnetic resonance imaging of sensorimotor cortex at 1.5 T. *Magn Reson Imaging* 14:51–58.
- Baudewig J, Kunkel M, Paulus W. 1997. Distribution of cortical activity in motor and sensory tasks focusing on the median nerve: a fMRI study. *Proc Internat Soc Magnet Res Med 5 Sci Meet Abstr no 702*.
- Büchert M, Schreiber A, Grimm C, Kristeva-Feige R, Otte M, Hupertz HJ, Hennig J, Mergner T, Lücking CH. 1997. Comparison of fMRI and high resolution EEG imaging with electric sensorimotoric stimulation of the median nerve. *Proc Internat Soc Magnet Res Med 5 Sci Meet Abstr no 703*.
- Cox RW, Hyde JS. 1997. Software tools for analysis and visualisation of fMRI data. *NMR in Biomed* 10:171–178.
- Curio G, Mackert BM, Burghoff M, Koetitz R, Abraham-Fuchs K, Härer W. 1994. Localization of evoked neuromagnetic 600 Hz activity in the cerebral somatosensory system. *Electroencephalogr Clin Neurophysiol* 91:483–487.
- Davis KD, Wood ML, Crawley AP, Mikulis DJ. 1995. fMRI of human somatosensory and cingulate cortex during painful electrical nerve stimulation. *NeuroReport* 7:321–325.
- Delberghe X, Mavrouidakis N, Zegers de Beyl D, Brunko E. 1990. The effect of stimulus frequency on post- and pre-central short-latency somatosensory evoked potentials (SEPs). *Electroencephalogr Clin Neurophysiol* 77:86–92.
- Edelman RR, Siewert B, Darby DG, Thangaraj V, Nobre AC, Mesulam MM, Warach S. 1994. Qualitative mapping of cerebral blood flow and functional localization with echo-planar MR imaging and signal targeting with alternating radio frequency. *Radiology* 192:513–520.
- Eisen A, Roberts K, Low M, Hoirch M, Lawrence P. 1984. Questions regarding the sequential neural generator theory of the somatosensory evoked potential raised by digital filtering. *Electroencephalogr Clin Neurophysiol* 59: 388–395.
- Emerson RG, Sgro JA, Pedley TA, Hauser WA. 1988. State-dependent changes in the N20 component of the median nerve somatosensory evoked potential. *Neurology* 38: 64–68.
- Emori T, Yamada T, Seki Y, Yasuhara A, Ando K, Honda Y, Leis AA, Vachaitmanont P. 1991. Recovery functions of fast frequency potentials in the initial negative wave of median SEP. *Electroencephalogr Clin Neurophysiol* 78:116–123.
- Florence SL, Jain N, Kaas JH. 1997. Plasticity of somatosensory cortex in primates. *Sem Neurosci* 9:3–12.
- Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. 1995. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med* 33:636–47.
- Gyngell ML, Bock C, Schmitz B, Hoehn-Berlage M, Hossmann KA. 1996. Variation of functional MRI signal in response to frequency of somatosensory stimulation in α -chloralose anesthetized rats. *Magn Reson Med* 36 (1): 13–15.
- Hammeke TA, Yetkin FZ, Mueller WM, Morris, GL, Haughton VM, Rao SM, Binder JR. 1994. Functional magnetic resonance imaging of sensorimotor stimulation. *Neurosurgery* 35:677–681.
- Hashimoto I, Mashiko T, Imada T. 1996. Somatic evoked high frequency magnetic oscillations reflect activity of inhibitory interneurons in the human somatosensory cortex. *Electroencephalogr Clin Neurophysiol* 100:189–203.
- Hume AL, Cant BR, Shaw NA. 1979. Central somatosensory conduction time in comatose patients. *Ann Neurol* 5:379–384.
- Ibañez V, Deiber MP, Sadato N, Toro C, Grissom J, Woods RP, Mazziotta JC, Hallett M. 1995. Effects of stimulus rate on regional cerebral blood flow after median nerve stimulation. *Brain* 118:1339–1351.
- Jueptner M, Weiller C. 1995. Review: does measurement of regional cerebral blood flow reflect synaptic activity? Implications for PET and fMRI. *Neuroimage* 2:148–156.
- Kadekaro M, Crane AM, Sokoloff L. 1985. Differential effects of electrical stimulation of sciatic nerve on metabolic activity in spinal cord and dorsal root ganglion in the rat. *Proc Natl Acad Sci USA* 82:6010–6013.
- Kim SG. 1995. Quantification of relative cerebral blood flow change by flow-sensitive alternating inversion recovery (FAIR) technique: application to functional mapping. *Magnet Reson Med* 34:293–301.
- Kurth R, Villringer K, Mackert BM, Schwiemann J, Braun J, Curio G, Villringer A, Wolf KJ. 1998. fMRI assessment of somatotopy in human Brodmann area 3b by electrical finger stimulation. *Neuroreport* 9:207–212.
- Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R, et al. 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci USA* 89: 5675–5679.
- Lüders H, Dinner DS, Lesser RP, Moris HH. 1986. Evoked potentials in cortical localization. *J Clin Neurophysiol* 3:75–84.
- Malonek D, Dirnagl U, Lindauer U, Yamada K, Kanno I, Grinvald A. 1997. Vascular imprints of neuronal activity: relationships between the dynamics of cortical blood flow, oxygenation, and volume changes following sensory stimulation. *Proc Natl Acad Sci USA* 94:14826–14831.
- Nudo RJ, Masterton RB. 1986. Stimulation-induced [14 C]2-deoxyglucose labeling of synaptic activity in the central auditory system. *J Comp Neurol* 245:553–565.
- Ogawa S, Lee TM, Kay AR, Tank DW. 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci USA* 87:9868–9872.
- Oldfield RC. 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9:97–113.
- Pratt H, Politoske D, Starr A. 1980. Mechanically and electrically evoked somatosensory potentials in humans: effects of stimulus presentation rate. *Electroencephalogr Clin Neurophysiol* 49:240–249.
- Puce A, Constable RT, Luby ML, McCarthy G, Nobre AC, Spencer DD, Gore JC, Allison T. 1995. Functional magnetic resonance imaging of sensory and motor cortex: comparison with electrophysiological localization. *J Neurosurg* 83:262–270.
- Ramsey NF, Kirkby BS, Van Gelderen P, Berman KF, Duyn JH, Frank JA, Mattay VS, Van Horn JD, Esposito G, Moonen CT, Weinberger DR. 1996. Functional mapping of human sensorimotor cortex with 3D BOLD fMRI correlates highly with H2(15)O PET rCBF. *J Cereb Blood Flow Metab* 16:755–764.
- Rao SM, Bandettini PA, Binder JR, Bobholz JA, Hammeke TA, Stein EA, Hyde JS. 1996. Relationship between finger movement rate and functional magnetic resonance signal change in human primary motor cortex. *J Cereb Blood Flow Metab* 16:1250–1254.

- Rao SM, Binder JR, Hammeke TA, Bandettini PA, Bobholz JA, Myklebust BM, Jacobson RD, Hyde JS. 1995. Somatotopic mapping of the human primary motor cortex with functional magnetic resonance imaging. *Neurology* 45:919–924.
- Righini A, de Divitiis O, Prinster A, Spagnoli D, Appollonio I, Bello L, Scifo P, Tomei G, Villani R, Fazio F, Leonardi M. 1996. Functional MRI: primary motor cortex localization in patients with brain tumors. *J Comput Assist Tomogr* 20:702–708.
- Rosen BR, Buckner RL, Dale AM. 1998. Event related functional MRI: past, present and future. *Proc Natl Acad Sci USA* 95:773–780.
- Sadato N, Ibañez V, Campbell G, Deiber MP, Le Bihan D, Hallett M. 1997. Frequency-dependent changes of regional cerebral blood flow during finger movements: functional MRI compared to PET. *J Cereb Blood Flow Metab* 17:670–679.
- Schlaug G, Sanes JN, Thangaraj V, Darby DG, Jancke L, Edelman RR, Warach S. 1996. Cerebral activation covaries with movement rate. *Neuroreport* 7:879–883.
- Woods RP, Cherry SR, Mazziotta JC. 1992. Rapid automated algorithm for aligning and reslicing PET images. *J Comput Assist Tomogr* 16:620–633.
- Yamada T, Kameyama S, Fuchigami Y, Nakazumi Y, Dickins QS, Kimura J. 1988. Changes of short latency somatosensory evoked potential in sleep. *Electroencephalogr Clin Neurophysiology* 70:126–136.
- Yarowsky P, Crane A, Sokoloff L. 1985. Metabolic activation of specific postsynaptic elements in superior cervical ganglion by antidromic stimulation of external carotid nerve. *Brain Res* 334:330–334.
- Yarowsky P, Kadekaro M, Sokoloff L. 1983. Frequency-dependent activation of glucose utilization in the superior cervical ganglion by electrical stimulation of cervical sympathetic trunk. *Proc Natl Acad Sci USA* 80:4179–4183.
- Yousry TA, Schmid UD, Alkadhi H, Schmidt D, Peraud A, Buettner A, Winkler P. 1997. Localization of the motor hand area to a knob on the precentral gyrus: a new landmark. *Brain* 120:141–157.
- Zhu XH, Kim SG, Andersen P, Ogawa S, Ugurbil K, Chen W. 1998. Simultaneous oxygenation and perfusion imaging study of functional activity in primary visual cortex at different visual stimulation frequency: quantitative correlation between BOLD and CBF changes. *Magn Reson Med* 40:703–711.