



Variability of BOLD response evoked by foot vibrotactile stimulation: Influence of vibration amplitude and stimulus waveform

C.M. Siedentopf,^{a,b,1} K. Heubach,^{b,c,1} A. Ischebeck,^d E. Gallasch,^e M. Fend,^e
F.M. Mottaghy,^f F. Koppelstaetter,^{a,b} I.A. Haala,^{a,b} B.J. Krause,^g S. Felber,^a
F. Gerstenbrand,^h and S.M. Golaszewski^{a,b,i,*}

^aDepartment of Radiology, Medical University, Innsbruck, Austria

^bfMRI-Lab, Department of Psychiatry, Medical University, Innsbruck, Austria

^cDepartment of Surgery, St. Neponuk Hospital, Erfurt, Germany

^dDepartment of Neurology, Medical University, Innsbruck, Austria

^eInstitute of Physiology, Medical University, Graz, Austria

^fDepartment of Nuclear Medicine, University Hospital, KU Leuven, Belgium

^gDepartment of Nuclear Medicine, Technical University, Munich, Germany

^hLudwig Boltzmann Institute for Restorative Neurology and Neuromodulation, Vienna, Austria

ⁱDepartment of Neurology, Paracelsus Medical University, Salzburg, Austria

Received 17 September 2007; revised 22 January 2008; accepted 19 February 2008

Available online 7 March 2008

The aim of the present was study to evaluate cortical and subcortical neural responses on vibrotactile stimulation of the foot and to assess somatosensory evoked BOLD responses in dependence of vibration amplitude and stimulus waveform.

Sixteen healthy male subjects received vibrotactile stimulation at the sole of the right foot. The vibration stimulus was delivered through a moving magnet actuator system (MMAS). In an event-related design, a series of vibration stimuli with a duration of 1 s and a variable interstimulus interval was presented. Four stimulation conditions were realized using a 2 (amplitudes 0.4 mm or 1.6 mm) × 2 (waveform sinusoidal or amplitude modulated) factorial design.

Stimulating with 0.4 mm amplitude compared to 1.6 mm stimulus amplitude more strongly activated the pre- and postcentral gyrus bilaterally and the right inferior, medial and middle frontal gyrus. In the reverse comparison significant differences were observed within the left inferior parietal lobule, the left superior temporal gyrus, and the left temporal transverse gyrus. In the comparison of sinusoidal versus modulated waveform and vice versa no significant activation differences were obtained. The inter-subject variability was high but when all four stimulation conditions were jointly analyzed, a significant activation of S1 was obtained for every single subject.

This study demonstrated that the BOLD response is modulated by the amplitude but not by the waveform of vibrotactile stimulation.

* Corresponding author. Department of Neurology, Paracelsus Medical University, Ignaz-Harrer-Strasse 79, 5020 Salzburg, Austria. Fax: +43 662 4483 3004.

E-mail address: S.Golaszewski@salk.at (S.M. Golaszewski).

¹ Authors contributed equally to the study.

Available online on ScienceDirect (www.sciencedirect.com).

Despite high inter-individual variability, the stimulation yielded reliable results for S1 on the single-subject level. Therefore, our results suggest that vibrotactile testing could evolve into a clinical tool in functional neuroimaging.

© 2008 Elsevier Inc. All rights reserved.

Keywords: fMRI; Vibrotactile stimulation of the foot; Vibration amplitude; Amplitude modulation; Sensorimotor cortex

Introduction

A multitude of afferent information reaches the sensorimotor cortex from the body surfaces. An important part of this information originates from cutaneous mechanoreceptors. Vibrotactile stimulation of these receptors results in specific cortical and subcortical BOLD activity changes associated with the hemodynamic response (BOLD, blood oxygenation level dependant) (Logothetis et al., 2004). Several studies yielded promising and reproducible results combining peripheral stimulation and fMRI for sensorimotor brain mapping (Sakai et al., 1995; Servos et al., 1998; Gelnar et al., 1998; Disbrow et al., 2000; Francis et al., 2000; Harrington et al., 2000; Golaszewski et al., 2002a,b, 2006).

A stimulation approach can be used to test the intactness of afferent pathways for the characterization of function in a lesioned brain. However, active motor paradigms such as finger-to-thumb or foot tapping are often not applicable for the functional assessment

of the sensorimotor network in the case of paretic or plegic extremities or in comatose or vegetative state patients.

For the clinical use of vibrotactile stimulation it is important to achieve a robust and reproducible BOLD response on the single-subject level.

With regard to amplitude modulation, a frequency range of 100 to 150 Hz seems to be advantageous to evoke robust steady state somatosensory evoked potentials (SEPs) (Snyder, 1992; Tobimatsu et al., 2000). The first harmonic component (1F) of vibratory SEPs was greatest at a modulation frequency of 21 Hz for the palm of the hand (Tobimatsu et al., 2000). For the sole of the foot, the greatest 1F was observed at modulation frequencies between 17 Hz and 30 Hz. Given these results we chose a modulation frequency of 25 Hz, expecting that somatosensory resonance might induce a stronger BOLD response than with non-modulated continuous stimulation.

In a feasibility study, Golaszewski et al. introduced a moving magnet actuator system (MMAS) for vibrotactile stimulation of the foot's sole which allows independent setting of frequency, amplitude, waveform and contact force. This MMAS was used in a first study with a sinusoidal stimulus at a frequency of 50 Hz and an amplitude of 1 mm. The fMRI measurement during vibrotactile stimulation revealed BOLD activity changes within the primary sensorimotor and secondary somatosensory cortex (Golaszewski et al., 2006). Based on the work of Tobimatsu it was hypothesized that the robustness and reproducibility of the BOLD response could be improved by amplitude modulation. The aim of the present study was to investigate the influence of vibration amplitude and stimulus waveform on the BOLD response. Following the results of Nelson et al. (2004) we hypothesized a greater BOLD response for increased vibration amplitudes. Given the results by Tobimatsu et al. (2000), we also expected an increase in the BOLD response for amplitude modulated stimulation due to a possible sensorimotor resonance effect.

Methods

16 healthy right handed male volunteers (age range 18–41 years, mean age 28.56 years, SD 5.86) without any history of neurological or psychiatric disorder participated in this study. All subjects gave their informed consent. The ethical committee of the Medical University of Innsbruck, Austria, approved the study protocol.

Experimental procedure

A moving magnet actuator system (MMAS) compatible with the scanning environment was used (Gallasch et al., 2006; Golaszewski et al., 2006). The MMAS ensures the effective transmission of a vibration stimulus by allowing the independent variation of vibration amplitude and frequency, stimulus waveform and contact force. The MMAS was positioned in front of the subject's right foot, behind the 20 mT isoline of the static magnetic field of the MRI scanner (Fig. 1). The indenter of the MMAS was brought into contact with the arch of the foot sole with an isotonic force of 5 N. This force was kept constant through the measurements. The contact area between the skin surface and the indenter was circular with an area of 19.63 cm² (diameter 5 cm). With this experimental setup, no interference between the MMAS and the MRI measurement and vice versa was detectable.

As a preliminary study with the MMAS (Gallasch et al., 2006) using a block design showed only a moderate BOLD response

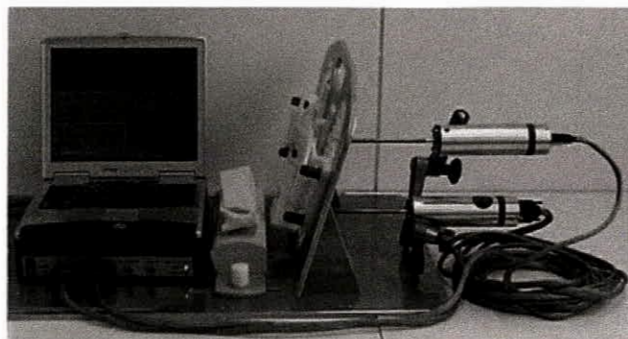


Fig. 1. A moving magnet actuator system (MMAS) ensures effective transmission of a vibration stimulus by allowing independent variation of vibration amplitude and frequency, stimulus waveform and contact force.

with a vibration frequency of 50 Hz and amplitude of 1 mm (Golaszewski et al., 2006), it was possible that these results were due to adaptation. Consequently, for this study, we chose an event-related design to increase the robustness and reproducibility of the cortical and subcortical BOLD responses.

To evoke responses from cutaneous mechanoreceptors a 100 Hz vibration stimulus was selected because this frequency is in the range of Pacinian corpuscles. Based on earlier experiments (Golaszewski et al., 2006) we chose amplitudes of 0.4 and 1.6 mm in this experiment to evaluate effects of different amplitudes. To evaluate effects of the stimulus waveform, sinusoidal and amplitude modulated was tested. The amplitude modulated waveform is represented by the analytical expression

$$s(t) = \frac{a}{2} [1 + \cos(2\pi f_{\text{mod}} t)] \sin(2\pi f_{\text{stim}} t)$$

with vibration amplitude a , modulation frequency f_{mod} and vibration frequency f_{stim} . On the basis of the studies of Snyder (1992) and Tobimatsu et al. (2000) the modulation frequency f_{stim} was selected as 25 Hz. With the multiplication term of $a/2$ the vibration amplitude of $s(t)$ is equal to the amplitude of the sinusoidal waveform.

A 2 (amplitudes 0.4 mm or 1.6 mm) × 2 (waveform sinusoidal or amplitude modulated) factorial design was used, yielding the following four stimulation conditions: sinusoidal waveform with vibration amplitude of 0.4 mm (SIN04), sinusoidal waveform with vibration amplitude of 1.6 mm (SIN16), amplitude modulated waveform with vibration amplitude of 0.4 mm (AM04), and amplitude modulated waveform with vibration amplitude of 1.6 mm (AM16). A fifth condition (no stimulation) was added to serve as a baseline condition (null event). In total, 250 trials were presented, 50 for each condition. The sequence of stimuli was randomized for each subject under the constraint that first order transition probabilities between conditions were held constant. Stimulus duration was 1 s. Between trials and during null-events, the vibration device maintained a constant contact force of 5 N. The inter stimulus interval was jittered between 1.5 and 4.5 s. On average every 3 s a stimulus was presented for 1 s.

MRI

All subjects were instructed to lie relaxed with their hands resting upon the abdomen and eyes closed during the fMRI measurement and not to think about anything. Foam padding and a

special helmet fixed to the head coil were used to limit involuntary head movements. The experiment was performed on a 1.5 T whole body scanner (Magnetom SONATA, Siemens, Germany) with an echo-planar capable gradient system (rise time 300 μ s, gradient strength 25 mT/ms) and a circular polarized head coil. For fMRI, we employed T2* weighted single shot echo-planar sequences (TR/TE/ α =0.96 ms/66 ms/90°, matrix=64×64, inplane resolution 3.75×3.75 mm, FOV=250 mm, thickness: 5 mm, gap: 1.25 mm). 24 axial slices covering the whole brain were acquired parallel to the bicommissural plane. The scan repetition time (TR) was 2.5 s including a delay of 50 ms. Per subject, 731 functional volumes were acquired during a single fMRI run resulting in a total scan time of 30.5 min.

Image analysis

Data analysis was performed using SPM2 (The Wellcome Department of Cognitive Neurology, London; <http://www.fil.ion.ucl.ac.uk/spm/>). The first five functional images of each subject were discarded from the analysis to ensure signal stabilization. The functional images were then realigned to the first image of the functional series. The anatomical image was coregistered to the functional image time series and normalized using the T1 template provided by SPM2. The functional images were normalized using the parameters gained from the normalization of the anatomical image. Finally, the functional data were smoothed with a Gaussian kernel of 8 mm FWHM. For statistical analysis, the delta function of stimulus

onsets for each of the five conditions was convolved with the canonical form of the hemodynamic response function (HRF) and its first time derivative as defined in SPM2. A statistical analysis was conducted on the basis of the general linear model as implemented in SPM2. A high pass filter of 50 Hz was used. Linear contrasts were calculated for the comparisons of the separate stimulation conditions to baseline (i.e. the null-events), as well as for the comparisons between stimulation conditions. The contrast images from the individual subject analyses were entered into a second level analysis to affect a random effects group analysis. Activations were reported for clusters that surpassed an initial threshold of $p < 0.005$ uncorrected, with a corrected p -value of $p < 0.05$ on cluster level. Anatomical locations of the activation foci were converted from MNI coordinates given by SPM2 to Talairach coordinates (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>) and determined using the atlas of Talairach and Tournoux (1988).

Results

Group analysis results

Comparisons to baseline

Comparisons of the four stimulation conditions to baseline yielded the following results (Table 1, Fig. 2): activations observed in all four stimulation conditions (SIN04, SIN16, AM04, and AM16) were within the postcentral gyrus, the inferior parietal lobule, the superior temporal gyrus and the temporal transverse

Table 1

Results from the group analysis for the contrasts of the four vibrotactile stimulation conditions against baseline (resting)

p corrected	Cluster size	p uncorrected	t -value	MNI coordinates			Side	Brodmann area	Anatomical location
				x	y	z			
SIN04									
0.000	275	0.000	6.84	48	-28	16	R	40, 41, 42, 13	GTs, GTT, LPi, GPoC, insula, thalamus, putamen
0.000	476	0.000	5.59	-64	-28	12	L	40, 41, 42, 13, 22, 1, 2, 43	GTs, GTT, LPi, GPoC, GTm, insula, thalamus
0.047	65	0.002	5.7	-12	-44	76	L	1, 2, 3, 4, 5, 7	GPoC, GPrC, LPs
SIN16									
0.000	644	0.000	9.05	-44	-24	20	L	40, 41, 42, 13, 22, 1, 2, 43, 27, 30, 38	GTs, GTT, Gsm, GTm, insula, GPoC, LPi, putamen, hippocampus, GH
0.000	500	0.000	7.02	64	-20	8	R	40, 41, 42, 13, 2, 43, 20, 21, 22, 27, 36, 38	GTs, GTT, GTm, insula, hippocampus, GPoC, LPi, GTi, GH, thalamus, putamen
0.004	115	0.000	5.97	-12	-44	76	L	1, 2, 3, 4, 5, 7	GPoC, GPrC, LPc, PCu
							R	5, 7	GPoC, PCu
AM04									
0.000	188	0.000	5.02	-40	-40	20	L	40, 41, 42, 43, 13, 39	GTs, GTT, Gsm, GA, insula, GPoC, LPi
0.000	156	0.000	4.9	40	-32	16	R	40, 41, 42, 2, 13, 22, 43	GTs, GTT, GPoC, LPi
0.039	62	0.002	3.95	-12	-40	76	L	1, 2, 3, 4, 5, 7	GPoC, GPrC, PCu, LPc
AM16									
0.000	381	0.000	9.18	-56	-28	16	L	40, 41, 42, 2, 13, 22, 43	GTs, GTT, insula, GPoC, LPi, putamen
0.000	298	0.000	6.44	52	-28	12	R	40, 41, 42, 13, 43	GTs, GTT, GPoC, LPi, hippocampus, insula, putamen, NC
0.04	75	0.002	6.01	-12	-44	76	L	1, 2, 3, 4, 5, 7	GPoC, GPrC, PCu, LPc

Clusters are reported as significant if they surpassed a threshold of $p < 0.005$, uncorrected, with p -value of $p < 0.05$, corrected on cluster level.

BA = Brodmann area; R = right hemisphere; L = left hemisphere; MNI = Montreal Neurological Institute; GPrC = precentral gyrus; GPoC = postcentral gyrus; GTs = superior temporal gyrus; GTm = middle temporal gyrus; GTi = inferior temporal gyrus; GTT = temporal transverse gyrus; LPi = inferior parietal lobule; LPs = superior parietal lobule; GA = angular gyrus; Gsm = supramarginal gyrus; GF = fusiform gyrus; Cu = cuneus; PCu = precuneus; GH = parahippocampal gyrus; LPc = paracentral gyrus; NC = caudate nucleus; GFi = inferior frontal gyrus; GFm = middle frontal gyrus; GFd = medial frontal gyrus; GL = lingual gyrus; mGC = middle cingulate gyrus.

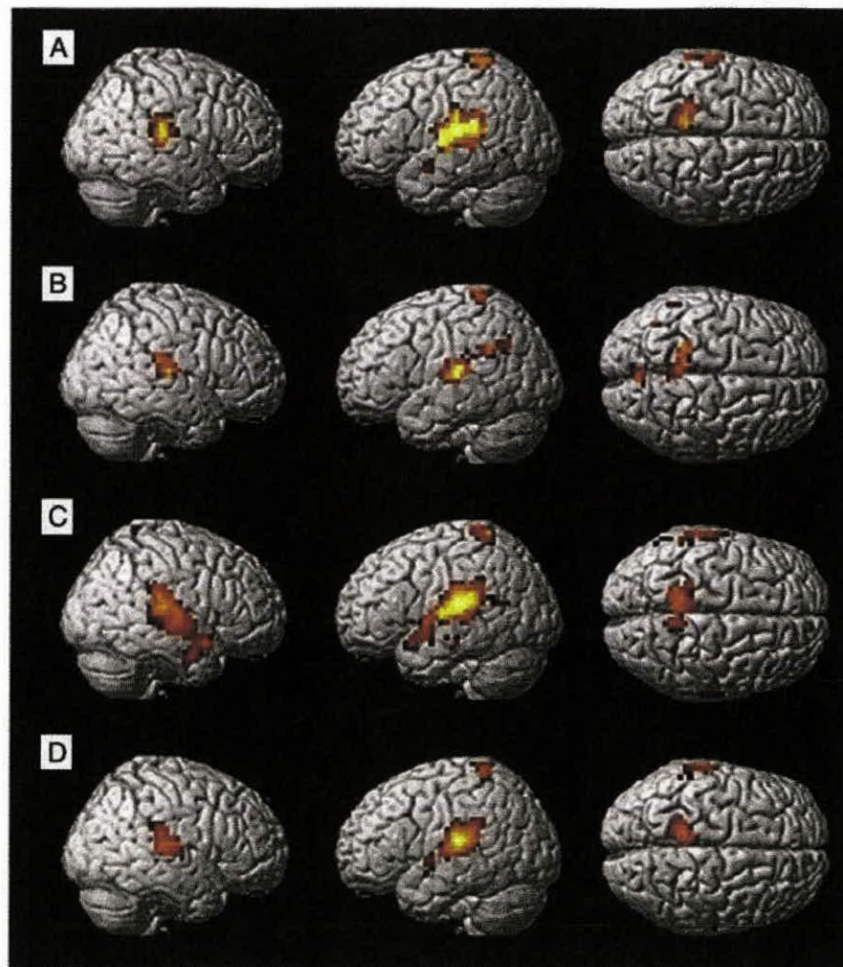


Fig. 2. Activation clusters for the random effect between group analysis results detected for the contrasts of the images acquired during vibrotactile stimulation and resting condition (A: 0.4 mm amplitude and sinusoidal waveform; B: 0.4 mm amplitude and amplitude modulated waveform; C: 1.6 mm amplitude and sinusoidal waveform; and D: 1.6 mm amplitude and amplitude modulated waveform). BOLD response is reported for clusters that surpassed an uncorrected threshold of $p < 0.005$ and a corrected p -value of $p < 0.05$ on cluster level.

gyrus, bilaterally. Additional activation foci were observed in SIN04: bilaterally within the insula and the thalamus, as well as within the left precentral gyrus, the left middle temporal gyrus, the left superior parietal lobule and within the right putamen. For SIN16, additional BOLD activity changes were observed bilaterally, within the middle temporal gyrus, precuneus, insula, parahippocampal and

hippocampal gyrus and the putamen. Further activations were observed within the right inferior temporal gyrus, the right paracentral gyrus, the right thalamus as well as the left precentral gyrus and supramarginal gyrus. For AM04, additional BOLD activity changes were observed within the left precentral gyrus, the left angular gyrus, the left supramarginal gyrus, the left superior parietal lobule, the left

Table 2
Results from the group analysis for comparison between vibrotactile stimulation conditions

p corrected	Cluster size	p uncorrected	t -value	MNI coordinates			Side	Brodmann area	Anatomical location
				x	y	z			
<i>0.4 mm amplitude versus 1.6 mm amplitude</i>									
0.000	225	0.000	4.99	36	-16	36	R	3, 2, 1, 6, 4, 44	GPoC, GPrC, GFs, GFi, GFd
0.000	150	0.000	4.94	-48	-16	56	L	3, 2, 1, 6, 4	GPoC, GPrC, GFs
<i>1.6 mm amplitude versus 0.4 mm amplitude</i>									
0.001	119	0.000	5	-48	-28	20	L	40, 41, 42, 22	GTs, GTT, LPi, insula, hippocampus

Clusters are reported as significant if they surpassed a threshold of $p < 0.005$, uncorrected, with p -value of $p < 0.05$, corrected on cluster level.

BA = Brodmann area; R = right hemisphere; L = left hemisphere; MNI = Montreal Neurological Institute; GPrC = precentral gyrus; GPoC = postcentral gyrus; GTs = superior temporal gyrus; GTm = middle temporal gyrus; GTi = inferior temporal gyrus; GTT = temporal transverse gyrus; LPi = inferior parietal lobule; LPs = superior parietal lobule; GA = angular gyrus; Gsm = supramarginal gyrus; GF = fusiform gyrus; Cu = cuneus; PCu = precuneus; GH = parahippocampal gyrus; LPc = paracentral gyrus; NC = caudate nucleus; GFi = inferior frontal gyrus; GFm = middle frontal gyrus; GFd = medial frontal gyrus; GFs = superior frontal gyrus; GL = lingula gyrus; mGC = middle cingulate gyrus.

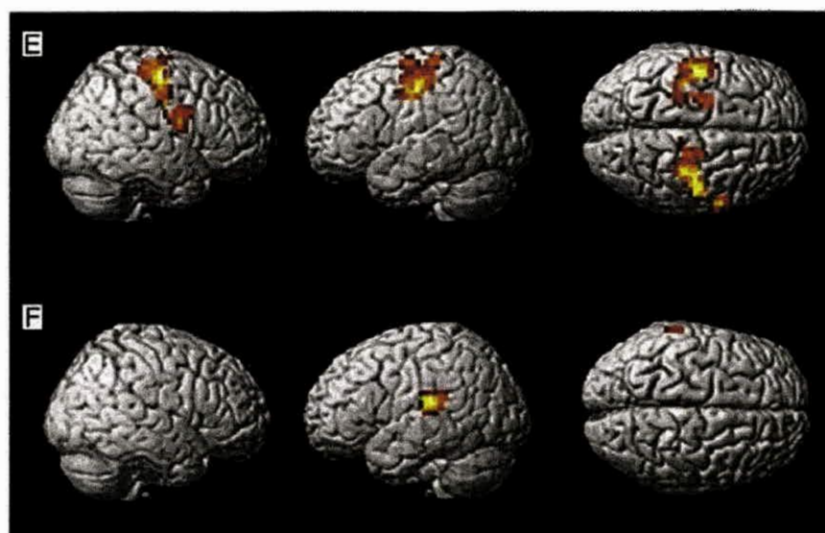


Fig. 3. Activation clusters for the random effect between group analysis results (E: 0.4 mm amplitude versus 1.6 mm amplitude; F: 1.6 mm amplitude versus 0.4 mm amplitude) detected for the contrasts of the images acquired during vibrotactile stimulation and resting condition. BOLD response is reported for clusters that surpassed an uncorrected threshold of $p < 0.005$ and a corrected p -value of $p < 0.05$ on cluster level.

precuneus as well as the left insula. For AM16, additional BOLD activity changes were observed bilaterally within the putamen and insula, as well as within the left precentral gyrus, the left paracentral gyrus, the left precuneus, the right caudate nucleus and the right hippocampal gyrus.

Comparisons between stimulation conditions

When the 0.4 mm amplitude (SIN04 and AM04) was compared to the 1.6 mm amplitude (SIN16 and AM16) stronger activations were observed within the post- and precentral gyrus bilaterally extending to the right inferior, medial and middle frontal gyrus. The reverse comparison yielded significantly stronger activations within the left inferior parietal lobule, extending to the superior temporal gyrus, and the temporal transverse gyrus (Table 2, Fig. 3). No significant differences were observed, however, between stimulation with amplitude modulation (AM04 and AM16) and sinusoidal amplitude (SIN04 and SIN16).

Single-subject analysis results

No single condition (SIN04, SIN16, AM04, or AM16) yielded significant activation within S1 for every subject. When the four conditions were analyzed jointly, however, a significant activation within the contralateral S1 was obtained for each subject.

Discussion

With this study we could demonstrate that the BOLD response is influenced by the amplitude of the vibrotactile stimulation. However, the stimulus waveform did not have a significant influence.

Vibration amplitude

Interestingly, stimulation with high vibration amplitude (SIN16, AM16) was found to decrease rather than increase cerebral activation within the primary somatosensory, primary motor and premotor cortices compared to stimulation with low amplitude (SIN04, AM04). These results were in contrast to the results

obtained by Nelson et al. (2004) who observed a direct increasing stimulus-response-relationship between vibration amplitude and BOLD response within primary and secondary somatosensory regions for thumb vibration. Nelson et al. used a passive vibration frequency of 20 Hz, whereas we applied a stimulation frequency of 100 Hz. This could indicate that the vibration frequency is a critical determinant for the perception of amplitude. The different results observed by Nelson et al. might also be due to hand stimulation, whereas we used foot stimulation. There are a greater number of mechanoreceptors in the hand than in the foot. It is possible that a different density of mechanoreceptors is associated with different stimulus-response properties.

Another reason for the decrease in activation with increasing amplitude might be attention. An influence of attention on somatosensory responses has been reported repeatedly in humans (Meyer et al., 1991; Mima et al., 1998; Staines et al., 2002). In the present study, subjects were explicitly instructed to relax. However, we cannot exclude that they attended differently to different stimulus amplitudes. They might have attended more to the vibration stimuli with smaller amplitude. This might have modulated the BOLD response in somatosensory areas.

Our results fit, however, with other findings. In a study by Jahn et al. (2004) a decrease in cerebral activity for imagining of walking and running compared with standing was demonstrated. This was interpreted as being due to a compensatory decrease of cerebral activity within the somatosensory cortex to prevent cortical interference with the optimized spinal motor patterns and sensations in automated locomotion like running or walking. Jahn et al. assumed that this indicates a hierarchical organization of posture and locomotion with different cortical centers being switched on and off in a task-specific manner (Jahn et al., 2004). On the basis of this reasoning an increased stimulation amplitude at the foot could lead to increased inhibition with a lower BOLD response when compared to lower stimulation amplitudes.

The inverse contrast, higher versus lower vibration amplitude, elicited significant activation within the primary auditory cortex. This activation might be due to the perception of the noise generated by the stimulation device, either directly or by osseous transmission.

Amplitude modulation

In contrast to Tobimatsu et al. (2000), who reported stronger activation within primary somatosensory cortex for foot vibration using amplitude modulation frequencies between 17 Hz and 30 Hz, we did not observe an effect of amplitude modulation on BOLD activity changes using a modulation frequency of 25 Hz. As Tobimatsu et al. also reported different tuning peaks for individual subjects, it is possible that optimal modulation frequencies differ between individuals. In four out of the 16 volunteers of the present study, we observed stronger activation within primary and/or secondary somatosensory cortex for amplitude modulation compared to sinusoidal stimulation. It is conceivable that the modulation frequency that we used was optimal only for these four volunteers. Inter-individual differences could be caused by difference in the receptors situated in the foot compared to the hand (Vedel and Roll, 1982; Ribot-Ciscar et al., 1989) and by differences in the sensitivity of sole afferences (Kennedy and Inglis, 2002).

Furthermore, the limited time resolution of the BOLD response might have prevented to detect more subtle signal changes due to amplitude modulation. The resonance phenomenon as described by Synder and later by Tobimatsu provides evidence for a strong grouping of sensory evoked spikes (and consequently field potentials) when the stimulus matches the tuning frequency. At other stimulation frequencies the same amount of spikes might be produced, but more random resulting in a wider spectral bandwidth. Integrated over the time this would yield the same BOLD response. Further studies with simultaneous EEG and fMRI would be necessary to clarify the neurodynamics of this stimulus evoked resonance phenomenon.

Neurophysiological interpretation

In this study we used vibration stimuli with a basis frequency of 100 Hz, a frequency that is in the susceptibility range of the vibration-sensitive Pacinian corpuscles (Harrington and Hunter, 2001). Pacinian corpuscles are located deep within the dermis and subcutis and have large, diffuse receptive fields (Talbot et al., 1968; Mountcastle 1984; Vallbo and Johansson, 1984). Vibrotactile stimuli are transmitted via the dorsal column pathway to the brainstem, where the afferent signals are switched to the second neuron that crosses to the contralateral side and reaches the thalamus. This input is mirrored in a significantly increased BOLD signal within the thalamus.

From the thalamus, there are widespread projections to the neocortex. In this study, significant BOLD signal increases were located contralaterally to the stimulated foot within the primary somatosensory cortex S1, which is known to receive input from cutaneous mechanoreceptors (Geyer et al., 1999; Kurth et al., 2000; Golaszewski et al., 2006). Pacinian corpuscles project diffusely contralaterally into Brodmann area 3a and 2 and bilaterally into S2, especially into Brodmann area 40 (Ferrington and Rowe, 1980; Gelnar et al., 1998; Maldjian et al., 1999; Francis et al., 2000) which is in accordance with the findings of this study. We observed S2 activation bilaterally with a lateralization to the left side. The S2 cortex projects to the insular cortex, which in turn innervates regions within the temporal lobe believed to be important for tactile memory. Accordingly, in our study BOLD activity changes were observed bilaterally within the insular region (BA 13) as well as bilaterally within the superior temporal region (BA 22, 41, 42), suggesting an orthodromic activation of the involved neural network.

The third major subdivision of the somatosensory cortex, the posterior parietal cortex (BA 5 and 7) was also activated. The posterior parietal cortex is related to associative functions.

The presented results demonstrated also BOLD activity changes within the motor cortex, especially contralaterally. BOLD response within the primary motor cortex M1 could be elicited by direct extero- and proprioceptive projections (Goldring and Ratcheson, 1972; Lucier et al., 1975; Hore et al., 1976; Asanuma et al., 1980; Murphy et al., 1975).

For the motor response to vibration, direct thalamocortical projections or transcortical loops (Evarts, 1973; Murphy et al., 1975) are likely to be responsible because they are involved in the vibratory tonic reflex. The stimulation paradigm used here most likely elicited the tonic vibratory reflex (TVR) in the bellies of the flexors of the digits I–V of the right foot (Burke et al., 1976; Golaszewski et al., 2002b) as well as in the bellies of the small muscles of the sole of the foot.

Single-subject evaluation

With respect to clinical applications, one aim of the study was to investigate the reliability of activation by vibrotactile stimulation on the single-subject level. Although all subjects showed comparable activation within the postcentral gyrus, as well as in parietal and temporal brain regions in all four vibrating conditions, none of the vibration conditions alone was able to induce a reliable activation within primary cerebral regions in each of the volunteers. 4 out of 16 volunteers showed no significant BOLD response in any of the four conditions, when analyzed separately. Only when all four conditions were analyzed jointly, significant activation within the primary somatosensory cortex was obtained for every singly subject. On the single-subject level, no single stimulation condition appeared to be superior compared to the other conditions. The single-subject results therefore showed considerable inter-individual variation. Nevertheless, the combination of various vibrating conditions led to reliable activation of S1 for every participant. The use of an event-related design had the advantage to allow the combination and comparison of different vibration stimuli within one experimental session. In a clinical setting, the use of different vibration conditions also could contribute in reducing adaptation. However, to ensure a robust result in individual patients, all stimulation conditions should be analyzed jointly.

In conclusion, the applied vibrotactile stimuli elicited reliable BOLD activity changes within the well-known sensorimotor network of cortical and subcortical structures as observed in the group analysis. While BOLD activity changes depended on amplitude height, the stimulus waveform did not yield significant activation differences in the group analysis. Stronger activation for amplitude modulation compared to sinusoidal stimulation in some individuals, however, suggests that the lack of significant results in the group analysis might be due to inter-individual processing differences, such as different frequency tuning curves. A combined analysis of all four conditions led to a reliable activation within primary somatosensory cortex S1 in all subjects, indicating that vibrotactile stimulation is suitable for clinical application. Nevertheless, research on further improvements of vibrotactile stimulation methods seems worthwhile to extend the suitability of this method to more fine-grained clinical applications. The present results therefore hold promise that vibrotactile stimulation could evolve into a promising and powerful tool in clinical functional neuroimaging, such as preoperative functional brain mapping, testing primary somatosensory cortex function in comatose patients,

monitoring of motor recovery after brain lesions and the planning of individual therapeutic strategies in neurorehabilitation.

Acknowledgments

This study was supported by the Austrian Ministry for Education, Science and Culture (Grants "Vibration of Foot Sole" and "MULTIVIB") and the Austrian National Bank (Grant Nr. 10109).

References

- Asanuma, H., Larsen, K., Yumiya, H., 1980. Peripheral input pathways to the monkey motor cortex. *Exp. Brain Res.* 38, 349–355.
- Burke, D., Hagbarth, K.E., Löfstedt, L., Wallin, B.G., 1976. The response of human muscle spindle endings to vibration of non-contracting muscles. *J. Physiol.* 261, 673–693.
- Disbrow, E., Roberts, T., Krubitzer, L., 2000. Somatotopic organization of cortical fields in the lateral sulcus of *Homo sapiens*: evidence for SII and PV. *J. Comp. Neurol.* 418, 1–21.
- Evarts, E.V., 1973. Motor cortex reflexes associated with learned movement. *Science* 179, 501–503.
- Ferrington, D.G., Rowe, M., 1980. Differential contributions to coding of cutaneous vibratory information by cortical somatosensory areas I and II. *J. Neurophysiol.* 43, 310–331.
- Francis, S.T., Kelly, E.F., Bowtell, R., Dunseath, W.J., Folger, S.E., McGlone, F., 2000. fMRI of the responses to vibratory stimulation of digit tips. *NeuroImage* 11, 188–202.
- Gallasch, E., Golaszewski, S.M., Fend, M., Siedentopf, C.M., Koppelstaetter, F., Eisner, W., Gerstenbrand, F., Felber, S.R., 2006. Contact force- and amplitude-controllable vibrating probe for somatosensory mapping of plantar afferences with fMRI. *J. Magn. Reson. Imaging* 24, 1177–1182.
- Gelnar, P.A., Krauss, B.R., Szeverenyi, N.M., Apkarian, A.V., 1998. Fingertip representation in the human somatosensory cortex: an fMRI study. *NeuroImage* 7, 261–283.
- Geyer, S., Schleicher, A., Zilles, K., 1999. Areas 3a, 3b, and 1 of human primary somatosensory cortex. Part 1. Micro structural organization and interindividual variabilities. *NeuroImage* 10, 63–83.
- Golaszewski, S.M., Zschiegner, F., Siedentopf, C.M., Unterrainer, J., Sweeney, R.A., Eisner, W., Unterrainer, J., Lechner-Steinleitner, S., Mottaghy, F.M., Felber, S., 2002a. A new pneumatic vibrator for functional magnetic resonance imaging of the human sensorimotor cortex. *Neurosci. Lett.* 324, 125–128.
- Golaszewski, S.M., Siedentopf, C.M., Baldauf, E., Koppelstaetter, F., Eisner, W., Unterrainer, J., Guendisch, G.M., Mottaghy, F.M., Felber, S.R., 2002b. Functional magnetic resonance imaging of the human sensorimotor cortex using a novel vibrotactile stimulator. *NeuroImage* 17, 421–430.
- Golaszewski, S.M., Siedentopf, C.M., Koppelstaetter, F., Fend, M., Ischebeck, A., Gonzalez-Felipe, V., Haala, I., Struhal, W., Mottaghy, F.M., Gallasch, E., Felber, S.R., Gerstenbrand, F., 2006. Human brain structures related to plantar vibrotactile stimulation: a functional magnetic resonance imaging study. *NeuroImage* 29, 923–929.
- Goldring, S., Ratcheson, R., 1972. Human motor cortex: sensory input data from single neuron recordings. *Science* 175, 1493–1495.
- Harrington, G.S., Hunter III, D.J., 2001. fMRI mapping of the somatosensory cortex with vibratory stimuli. Is there a dependency on stimulus frequency? *Brain Res.* 897, 188–192.
- Harrington, G.S., Wright, C.T., Downs III, J.H., 2000. A new vibrotactile stimulator for functional MRI. *Hum. Brain Mapp.* 3, 140–145.
- Hore, J., Preston, J.B., Cheney, P.D., 1976. Responses of cortical neurons (areas 3a and 4) to ramp stretch of hind limb muscles in the baboon. *J. Neurophysiol.* 39, 484–500.
- Jahn, K., Deutschländer, A., Stephan, T., Strupp, M., Wiesmann, M., Brandt, T., 2004. Brain activation patterns during imagined stance and locomotion in functional magnetic resonance imaging. *NeuroImage* 22, 1722–1731.
- Kennedy, P.M., Inglis, J.T., 2002. Distribution and behavior of glabrous cutaneous receptors in the human foot sole. *J. Physiol.* 538, 995–1002.
- Kurth, R., Villringer, K., Curio, G., Wolf, K.J., Krause, T., Repenthin, J., Schwiemann, J., Deuchert, M., Villringer, A., 2000. fMRI shows multiple somatotopic digit representations in human primary somatosensory cortex. *NeuroReport* 11, 1487–1491.
- Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., Oeltermann, A., 2004. Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412, 150–157.
- Lucier, G.E., Rüegg, D.C., Wiesendanger, M., 1975. Responses of neurons in motor cortex and in area 3A to controlled stretches of forelimb muscles in cebus monkey. *J. Physiol.* 251, 833–853.
- Maldjian, J.A., Gottschalk, A., Patel, R.S., Pincus, D., Detre, J.A., Alsop, D.C., 1999. Mapping of secondary somatosensory cortex activation induced by vibrational stimulation: an fMRI study. *Brain Res.* 824, 291–295.
- Meyer, E., Ferguson, S.S., Zatorre, R.J., Alivisatos, B., Marrett, S., Evans, A.C., Hakim, A.M., 1991. Attention modulates somatosensory cerebral blood flow response to vibrotactile stimulation as measured by positron emission tomography. *Ann. Neurol.* 29, 440–443.
- Mima, T., Nagamine, T., Nakamura, K., Shibasaki, H., 1998. Attention modulates both primary and second somatosensory cortical activities in humans: a magnetoencephalographic study. *J. Neurophysiol.* 80, 2215–2221.
- Mountcastle, V.B. (Ed.), 1984. *Medical Physiology, Sensory Receptors and Neural Encoding: Introduction to Sensory Processes*. C.V. Mosby, St. Louis.
- Murphy, J.T., Wong, Y.C., Kwan, H.C., 1975. Afferent–efferent linkages in motor cortex for single forelimb muscles. *J. Neurophysiol.* 38, 990–1014.
- Nelson, A.J., Staines, W.R., Graham, S.J., McLroy, W.E., 2004. Activation in SI and SII; the influence of vibrotactile amplitude during passive and task-relevant stimulation. *Cogn. Brain Res.* 19, 174–184.
- Ribot-Ciscar, E., Vedel, J.P., Roll, J.P., 1989. Vibration sensitivity of slowly and rapidly adapting cutaneous mechanoreceptors in the human foot and leg. *Neurosci. Lett.* 104, 130–135.
- Sakai, K., Watanabe, E., Onodera, Y., Itagaki, H., Yamamoto, E., Koizumi, H., Miyashita, Y., 1995. Functional mapping of the human somatosensory cortex with echo-planar MRI. *Magn. Reson. Med.* 33, 736–743.
- Servos, P., Zacks, J., Rummelhart, D.E., Glover, G.H., 1998. Somatotopy of the human arm using fMRI. *NeuroReport* 9, 605–609.
- Snyder, A.Z., 1992. Steady-state vibration evoked potentials: description of technique and characterization of responses. *Electroencephalogr. Clin. Neurophysiol.* 84, 257–286.
- Staines, W.R., Graham, S.J., Black, S.E., McLroy, W.E., 2002. Task-relevant modulation of contralateral and ipsilateral primary somatosensory cortex and the role of a prefrontal-cortical sensory gating system. *NeuroImage* 15, 190–199.
- Talairach, J., Tournoux, P., 1988. *Co-planar Stereotaxic Atlas of the Human Brain: 3-dimensional Proportional System: An Approach to Cerebral Imaging*. Georg Thieme Verlag, Stuttgart and New York.
- Talbot, W.H., Darian-Smith, I., Kornhuber, H.H., Mountcastle, V.B., 1968. The sense of flutter-vibration: comparison of the human capacity with response patterns of mechanoreceptive afferents from the monkey hand. *J. Neurophysiol.* 31, 301–334.
- Tobimatsu, S., Zhang, Y.M., Suga, R., Kato, M., 2000. Differential temporal coding of the vibratory sense in the hand and foot in man. *Clin. Neurophysiol.* 111, 398–404.
- Vallo, A.B., Johansson, R.S., 1984. Properties of cutaneous mechanoreceptors in the human hand related to touch sensation. *Hum. Neurobiol.* 3, 3–14.
- Vedel, J.P., Roll, J.P., 1982. Response to pressure and vibration of slowly adapting cutaneous mechanoreceptors in the human foot. *Neurosci. Lett.* 34, 289–294.

PubMed

Format: Abstract

Full text links

Neuroimage. 2008 Jun;41(2):504-10. doi: 10.1016/j.neuroimage.2008.02.049. Epub 2008 Mar 7.

ELSEVIER
FULL-TEXT ARTICLE

Variability of BOLD response evoked by foot vibrotactile stimulation: influence of vibration amplitude and stimulus waveform.

Siedentopf CM¹, Heubach K, Ischebeck A, Gallasch E, Fend M, Mottaghy FM, Koppelstaetter F, Haala IA, Krause BJ, Felber S, Gerstenbrand F, Golaszewski SM.

Author information

1 Department of Radiology, Medical University, Innsbruck, Austria.

Abstract

The aim of the present was study to evaluate cortical and subcortical neural responses on vibrotactile stimulation of the food and to assess somatosensory evoked BOLD responses in dependence of vibration amplitude and stimulus waveform. Sixteen healthy male subjects received vibrotactile stimulation at the sole of the right foot. The vibration stimulus was delivered through a moving magnet actuator system (MMAS). In an event-related design, a series of vibration stimuli with a duration of 1 s and a variable interstimulus interval was presented. Four stimulation conditions were realized using a 2 (amplitudes 0.4 mm or 1.6 mm) x 2 (waveform sinusoidal or amplitude modulated) factorial design. Stimulating with 0.4 mm amplitude compared to 1.6 mm stimulus amplitude more strongly activated the pre- and postcentral gyrus bilaterally and the right inferior, medial and middle frontal gyrus. In the reverse comparison significant differences were observed within the left inferior parietal lobule, the left superior temporal gyrus, and the left temporal transverse gyrus. In the comparison of sinusoidal versus modulated waveform and vice versa no significant activation differences were obtained. The inter-subject variability was high but when all four stimulation conditions were jointly analyzed, a significant activation of S1 was obtained for every single subject. This study demonstrated that the BOLD response is modulated by the amplitude but not by the waveform of vibrotactile stimulation. Despite high inter-individual variability, the stimulation yielded reliable results for S1 on the single-subject level. Therefore, our results suggest that vibrotactile testing could evolve into a clinical tool in functional neuroimaging.

PMID: 18424181 DOI: [10.1016/j.neuroimage.2008.02.049](https://doi.org/10.1016/j.neuroimage.2008.02.049)

[Indexed for MEDLINE]

