

## BOLD Adaptation in Vibrotactile Stimulation: Neuronal Networks Involved in Frequency Discrimination

Yiwen Li Hegner,<sup>1,2,3</sup> Ralf Saur,<sup>4</sup> Ralf Veit,<sup>1</sup> Raymond Butts,<sup>3</sup> Susanne Leiberg,<sup>5</sup> Wolfgang Grodd,<sup>4</sup> and Christoph Braun<sup>1,2</sup>

<sup>1</sup>Institute of Medical Psychology and Behavioral Neurobiology, <sup>2</sup>MEG-Center, <sup>3</sup>Graduate School of Neural and Behavioural Sciences, International Max Planck Research School, and <sup>4</sup>Neuroradiology, University Clinics Tübingen, University of Tübingen, Tübingen, Germany; and <sup>5</sup>Department of Psychiatry and Psychotherapy, University Hospital Aachen, Aachen, Germany

Submitted 13 June 2006; accepted in final form 19 October 2006

**Li Hegner Y, Saur R, Veit R, Butts R, Leiberg S, Grodd W, Braun C.** BOLD adaptation in vibrotactile stimulation: neuronal networks involved in frequency discrimination. *J Neurophysiol* 97: 264–271, 2007. First published October 25, 2006; doi:10.1152/jn.00617.2006. The present functional magnetic resonance imaging (fMRI) study investigated human brain regions subserving the discrimination of vibrotactile frequency. An event-related adaptation paradigm was used in which blood-oxygen-level-dependent (BOLD) responses are lower to same compared with different pairs of stimuli (BOLD adaptation). This adaptation effect serves as an indicator for feature-specific responding of neuronal subpopulations. Subjects had to discriminate two vibrotactile stimuli sequentially applied with a delay of 600 ms to their left middle fingertip. The stimulus frequency was in the flutter range of 18–26 Hz. In half of the trials, the two stimuli possessed identical frequency (same), whereas in the other half, a frequency difference of  $\pm 2$  Hz was used (diff). As a result, BOLD adaptation was observed in the contralateral primary somatosensory cortex (S1), precentral gyrus, superior temporal gyrus (STG); ipsilateral insula as well as bilateral secondary somatosensory cortex and supplementary motor area. When statistically comparing the BOLD time courses between same and diff trials in these cortical areas, it was found that the vibrotactile BOLD adaptation is initiated in the contralateral S1 and STG simultaneously. These findings suggest that the cortical areas responsive to the frequency difference between two serially presented stimuli sequentially process the frequency of a vibrotactile stimulus and constitute a putative neuronal network underlying human vibrotactile frequency discrimination.

### INTRODUCTION

To unravel the neural mechanisms that subserve the discrimination of two stimuli on a certain dimension, it is pertinent to identify the cortical areas that encode this specific stimulus dimension. In the somatosensory modality, ample research has been conducted probing the frequency discrimination of vibrotactile stimuli and therewith the representation of vibrotactile frequency. Frequency discrimination of vibrotactile stimuli has been studied intensively in primate single-cell recordings (Luna et al. 2005; Mountcastle et al. 1969; Recanzone et al. 1992; Romo and Salinas 2003; Romo et al. 2006; Talbot et al. 1968) as well as in psychophysical experiments in humans and monkeys (Harris 2006; Harris et al. 2001, 2002; LaMotte and Mountcastle 1975; Mountcastle et al. 1990). Via microstimulation, Romo and colleagues indicated that quickly adapting (QA) neurons in Brodmann area 3b of the primary somatosensory cortex (S1) in monkeys are directly involved in inducing

the perception of vibrotactile flutter (Romo et al. 1998, 2000). Many of these neurons show phase-locked firing (Mountcastle et al. 1990), where the firing rate seems to encode the vibrotactile frequency (Hernandez et al. 2000; Salinas et al. 2000) in a spike count code (Luna et al. 2005). Through carefully conducted neurophysiological experiments in behaving monkeys, Romo's research group has accumulated information on the cortical areas involved in vibrotactile frequency discrimination. They have shown that S1 drives and works closely with higher cortical areas like secondary somatosensory cortex (S2), premotor cortex as well as prefrontal cortex during performance of a sensory discrimination task (Romo et al. 2002a,b, 2004, 2006; Zainos et al. 1997). Human psychophysical studies of Harris and colleagues have additionally suggested that S1 stores transient vibrotactile information (Harris et al. 2002) in a somatotopic fashion (Harris et al. 2001). They found that subjects performed better when a pair of vibrotactile stimuli was delivered to the same finger tip or to the corresponding finger of the opposite hand than when the second stimulus was applied to a distant finger (Harris et al. 2001). Furthermore, they demonstrated that applying transcranial magnetic stimulation (TMS) to human contralateral S1 during the early phase (300 or 600 ms) of the retention period of a vibrotactile discrimination task diminished the subjects' performance (Harris et al. 2002). Interestingly, applying TMS during the later phase (900 or 1,200 ms) did not influence subjects' performance. This indicates that the vibrotactile information might reside in S1 for around 600 ms and then might be transferred to other cortical areas in the consecutive discrimination processes.

As intriguing and important these TMS results are, it is not possible to precisely circumscribe the cortical sites that are affected by TMS and to differentially determine its influence on the ongoing cortical processes. Moreover, like single-cell recordings, which are rarely feasible in humans, both methods are confined to preselected cortical areas and usually do not permit a simultaneous assessment of a larger neuronal network. Therefore we decided to study vibrotactile discrimination by whole-brain fMRI using a blood-oxygen-level-dependent (BOLD) adaptation paradigm. Until now hemodynamic and electromagnetic brain-imaging studies investigating whole-brain activity during vibrotactile frequency discrimination tasks are scarce. Thus the human neural network underlying vibrotactile frequency processing has only been incompletely characterized.

Address for reprint requests and other correspondence: Y. Li Hegner, MEG-Center, Otfried-Müller-Str. 47, 72076 Tübingen, Germany (E-mail: yiwen.li@med.uni-tuebingen.de).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

In humans, fMRI adaptation paradigms have been employed to study the stimulus feature specificity of neuronal populations (Grill-Spector and Malach 2001; Grill-Spector et al. 2006; Schacter and Buckner 1998). These paradigms take advantage of the fact that repeated presentation of identical stimuli decreases the activity of locally clustered neurons encoding and processing those stimuli. To explore which cortical areas encode and further process a certain stimulus feature, two stimuli, which are either identical or different in one specific feature, are sequentially presented with an interstimulus interval (ISI) in the range of several hundred milliseconds (Altmann et al. 2004; Kourtzi and Huberle 2005; Kourtzi and Kanwisher 2001). Then the BOLD responses to the two types of stimulus pairs can be compared, assuming that neuronal assemblies that are selective for the varied stimulus feature should show no response reduction to stimulus pairs differing in the feature, whereas the neurons that are invariant to the stimulus change would exhibit response adaptation. In studying such adaptation effects, it is possible to further disentangle neuronal properties with a spatial resolution superior to that of conventional fMRI approaches with standard threshold evaluation (Naccache and Dehaene 2001). Many studies have applied fMRI adaptation paradigm to reveal the cortical areas that encode specific stimulus features. However, most of these imaging experiments have been performed in the visual modality (Grill-Spector et al. 2006; Kourtzi and Kanwisher 2001; Tootell et al. 1995; Vuilleumier et al. 2002).

Here we investigated which cortical areas exhibit response adaptation in a vibrotactile frequency discrimination task. This could further elucidate the underlying cortical network involved in vibrotactile frequency processing. In single-cell recordings, vibrotactile response adaptation has been shown to be a central process for both slowly adapting (SA) and QA neurons in decerebrated and anesthetized cats (O'Mara et al. 1988) as well as for QA neurons in S1 of anesthetized monkeys (Whitsel et al. 2001, 2003). Additionally, in humans, a strong decrease of electroencephalographic (EEG) transient response has been shown to be evoked by repetitive 60-Hz vibrotactile stimulation (Hari 1980). Further support for selective adaptation of vibrotactile frequency has been provided by a recent single-unit recording study demonstrating a putative frequency-tuning somatotopic map in rat S1 ("barrel" cortex), corresponding to vibrissa tuning (Andermann et al. 2004).

In the current study, subjects were sequentially presented with two vibrotactile stimuli that either matched (same) or differed (diff) in their vibratory frequency. Given the logic of stimulus-specific adaptation, a decrease of the BOLD response to vibrotactile stimulus pairs of identical compared with differing vibratory frequency in a cortical area would implicate this region in the processing of vibrotactile frequency. It is assumed that the differential cortical responses of these areas to same and to diff stimuli pairs facilitate discrimination of vibrotactile frequency. To further characterize the cortical network underlying vibrotactile stimulus discrimination, we investigated its temporal properties, i.e., in which cortical areas the response adaptation commences and to which regions it is propagated. In line with previous studies (Harris 2006; Harris et al. 2001, 2002; Luna et al. 2005; Romo and Salinas 2003; Romo et al. 2002a,b, 2004, 2006; Zainos et al. 1997), we hypothesized to see BOLD adaptation in S1, S2, and higher cognitive areas such as premotor and prefrontal cortices. We

would expect to see S1 to be the region showing the earliest response adaptation since it is the first cortical area reached by somatosensory information. In addition, a very recent magnetoencephalography (MEG) study presenting evidence of superior temporal cortex activation during vibrotactile stimulation (Caetano and Jousmaki 2006) suggested that this area might also be involved. It would thus be very interesting to see whether auditory cortices are taking part in a vibrotactile frequency discrimination process.

## METHODS

### Participants

Ten healthy right-handed subjects [age:  $26 \pm 1.7$  (SD) yr, 5 females] participated in this study. Two subjects were excluded from data analysis due to excessive head motion. This study was compliant with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the protocol of human investigation was approved by the local ethics committee. Prior to fMRI data acquisition, subjects gave their written informed consent.

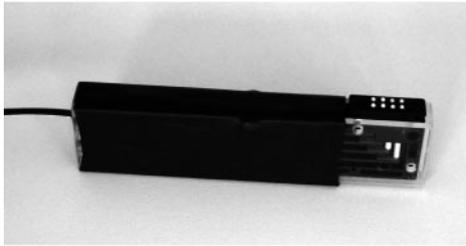
### Vibrotactile stimulation

The tactile vibration was provided by piezoelectric wafers (piezo: TeleSensory, CA; casing and electrical connectivity board: metec AG, Stuttgart, Germany) driven by 200-V pulses from custom-made amplifiers, which were controlled by a computer running on real-time operation system. As stimulus, a sinusoidal vibration modulated in amplitude was used. The carrier frequency of the sine wave was 150 Hz, and the modulation frequency was in the flutter range of 18–26 Hz with 2-Hz steps. We used similar AM in previous MEG studies to enhance the signal-to-noise ratio (Tan et al. 2004). Importantly, the vibratory perception is built on the modulation frequency but not the carrier frequency (Tobimatsu et al. 1999). The vibrating surface consisted of a panel of eight rods (rod size  $\varnothing$  1 mm,  $2 \times 4$  arrays, panel size:  $4 \times 8$  mm<sup>2</sup>, see Fig. 1A), ascending and descending simultaneously and causing a skin indentation of  $\sim 1.5$  mm. For each subject, the piezoelectric wafer case was attached to the left middle fingertip with the vibrating surface touching the glabrous skin with an equal and moderate force.

### Design

We used an event-related fMRI adaptation paradigm consisting of 48 trials. In each trial, two vibratory stimuli lasting 400 ms each were serially presented with a constant ISI of 600 ms (Fig. 1B). In a two-alternative forced-choice manner, subjects had to compare the vibrotactile frequency of the two stimuli and respond accordingly by pushing a button either with their left or right thumb (indicating either 1st or 2nd stimulus vibrated faster). The intertrial interval (ITI) was randomly set and varied from 2.35 to 24.85 s with an adjustment to the temporal jittering of the functional imaging trigger (mean ITI:  $8.8 \pm 5.2$  s). Additionally, two 12-s rest periods, one at the beginning and one at the end of the experiment, were added. In half of the trials, the stimuli possessed the same frequency (same: e.g., 18–18, 20–20, 22–22, 24–24, and 26–26 Hz), whereas in the other half, a frequency difference of  $\pm 2$  Hz was used (diff: equal number of "plus" and "minus" trials, e.g., 18–20, 20–18, 22–20, 22–24 Hz, etc.). Therefore the total input energy of both experimental conditions (same vs. diff) was balanced. The subjects were not informed about the possibility of stimulus pairs with equal frequency; instead they always had to decide which stimulus vibrated faster. Nevertheless, in the diff condition the 2-Hz frequency difference was already very challenging for the subjects to discriminate according to their subjective reports and our previous experiences. We resorted to this experimental design to get

A



B

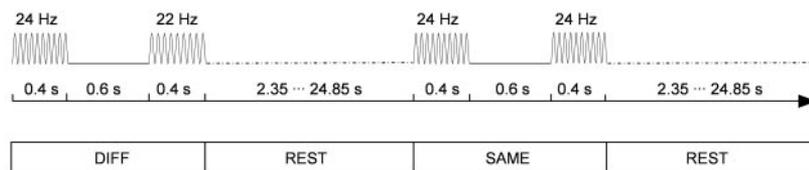


FIG. 1. Vibrotactile stimulation device and experimental design. *A*: tactile vibration was provided by piezoelectric wafers driven by custom-built amplifiers. The vibrating surface consists of a panel of 8 rods (rod size  $\varnothing$  1 mm,  $2 \times 4$  arrays, panel size:  $4 \times 8$  mm<sup>2</sup>), ascending and descending simultaneously and causing a skin indentation of  $\sim 1.5$  mm. *B*: complete trial consisted of 2 vibrotactile stimuli lasting 0.4 s each with an interstimulus interval (ISI) of 0.6 s. Subjects were asked to answer as soon as possible by pressing a button with the thumb (left or right hand) to indicate which 1 of the 2 stimuli had a higher vibratory frequency.

equal attention for trials of both conditions. However, by doing so, we also limited our analysis of the behavioral data because the answers for the same trials would always be wrong. The order of the trials was randomized and counterbalanced across subjects.

### Imaging

The experiment was conducted in a 1.5 T scanner (Siemens Sonata) using an echo planar imaging (EPI) sequence (TR = 3 s, TE = 49 ms, 166 volumes). The functional scan consisted of 36 axial slices (slice thickness: 3 mm) covering the whole brain with a planar resolution of  $3 \times 3$  mm<sup>2</sup> and an inter-slice gap of 0.99 mm. An anatomical T1-weighted image data set with an MPRAGE sequence with 1-mm isotropic resolution was additionally acquired for each subject directly after the functional imaging.

### Data analysis

The fMRI data were analyzed using Brain Voyager QX (Brain Innovation B.V., The Netherlands). Prior to analysis, the first three volumes were discarded. The preprocessing of the functional data included three-dimensional (3D) motion correction,  $8 \times 8 \times 8$ -mm Gaussian filter spatial smoothing, temporal high-pass filtering (cut-off frequency: 0.00613 Hz), and linear trend removal. Anatomical data were transformed into Talairach space, and the cortices were reconstructed for each subject. To achieve a better spatial correspondence mapping of cortical areas across subjects, each hemisphere was morphed into a spherical representation allowing a cortex-based inter-subject alignment among subjects (Fischl et al. 1999; van Atteveldt et al. 2004). As a result of intersubject alignment, group-averaged left and right hemispheres were created. After individual coregistration of functional and anatomical data, we used the correspondence mapping to align the time courses of the functional data.

We performed a multi-subject random-effect general linear model (GLM) analysis with one regressor for the vibrotactile stimulation during the same and diff trials. Because of the extended time course of the BOLD signal and the short ISI (0.6 s), the hemodynamic responses to the sequentially presented stimuli within a trial could not be resolved. Therefore the ISI was included in the modeling of stimulation, which had a total duration of 1.4 s and was convolved with a two-Gamma hemodynamic response function (response peak at 5 s). Then the activation map from the group random-effect analysis contrasting stimulation against rest condition was overlaid on the averaged left and right hemisphere to define the patches of interest (POIs,  $P < 0.003$ , uncorrected, cluster size:  $>50$  mm<sup>2</sup>). Based on the

information from the interindividual cortical alignment, we defined the individual POIs for each subject via the POIs of the group-averaged hemispheres. In this way, the POIs for each subject have equivalent anatomical locations.

We extracted the time course of the BOLD responses averaged from voxels within each POI of each subject. Event-related averaging (the mean of 3 s before the 1st stimulus onset was subtracted from the time course of each trial to get the percent BOLD signal change) was done separately for the two conditions (same vs. diff) for each POI across eight subjects. After selecting a peak BOLD response value (between 1 and 10 s after the 1st stimulus onset) from the same and diff time courses for every subject, we applied a one-sided paired-*t*-test for each POI to examine which brain areas responded significantly stronger to diff compared with same trials, i.e., which areas showed BOLD response adaptation.

## RESULTS

### Behavioral data

The average performance of the subjects was  $73 \pm 7.7\%$  correct for the diff condition. In the same trials, because the subjects were instructed to select a stimulus that vibrated higher, the answers were predetermined wrong. The mean response of  $49 \pm 9.9\%$  in the same condition indicates that subjects pressed both buttons equally often as a result of random decision. The mean reaction time (RT) for the same and diff condition was  $0.77 \pm 0.18$  and  $0.72 \pm 0.17$  s, respectively, without a significant difference between both conditions [ $t(7) = 1.32$ ;  $P = 0.23$ ].

### Functional imaging data

Contrasting the vibrotactile stimulation with the rest condition (Fig. 2), we found activation ( $P < 0.003$ , uncorrected, cluster size  $>50$  mm<sup>2</sup>) in the contralateral postcentral gyrus (S1, area 3b and 1), superior temporal gyrus (STG); ipsilateral lateral sulcus; bilateral thalamus, precentral gyrus (primary motor and premotor cortex), precentral sulcus, posterior parietal cortex, S2, insula, and SMA. All these areas were taken as POIs (Fig. 2) for individual subject analysis, and a one-sided paired-*t*-test (same vs. diff) was applied for each POI across subjects.

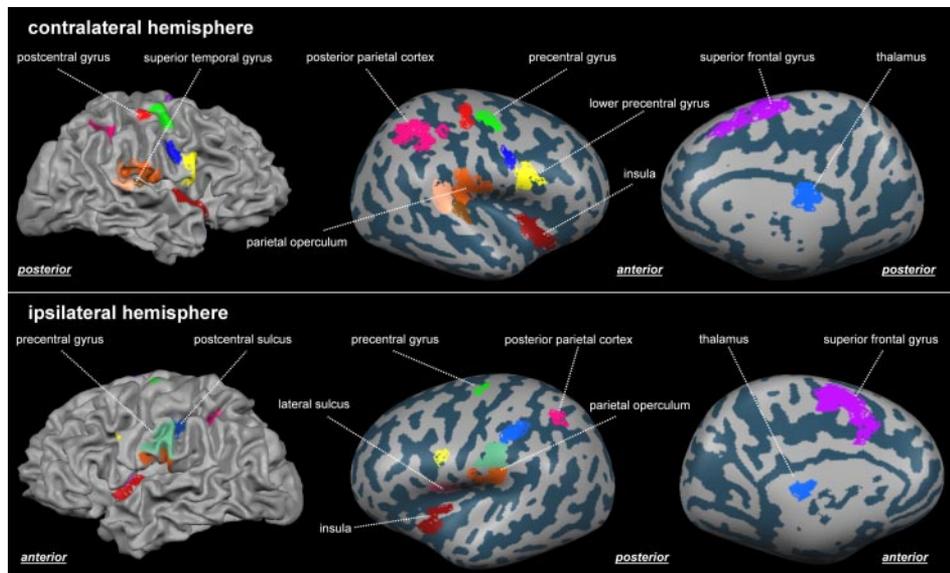


FIG. 2. Cortical activation map contrasting vibrotactile stimulation to rest period. The blood-oxygen-level-dependent (BOLD) activation is overlaid on the folded as well as inflated right and left hemispheres of 1 subject (light gray depicts gyri and dark gray depicts sulci). The activated areas are filled in with different colors to represent the defined patches of interest (POIs,  $P < 0.003$ , uncorrected, cluster size:  $>50 \text{ mm}^2$ ). The POIs that showed significant BOLD response adaptation are: contralateral central sulcus and postcentral gyrus (S1,  $P < 0.001$ ), precentral gyrus (primary motor and premotor cortex,  $P < 0.05$ ), parietal operculum of the lateral sulcus (S2,  $P < 0.05$ ), superior temporal gyrus (STG,  $P < 0.05$ ), superior frontal gyrus (SMA,  $P < 0.01$ ) and ipsilateral parietal operculum of the lateral sulcus (S2,  $P < 0.05$ ), insula ( $P < 0.05$ ), superior frontal gyrus (SMA,  $P < 0.05$ ).

The brain regions responding significantly stronger to diff compared with same condition (i.e., the areas showing BOLD response adaptation) were: contralateral S1 [ $t(7) = 5.44$ ,  $P < 0.001$ ], precentral gyrus [ $t(7) = 3.48$ ,  $P < 0.05$ ], STG [ $t(7) = 3.24$ ,  $P < 0.05$ ]; ipsilateral insula [ $t(7) = 3.16$ ,  $P < 0.05$ ] and bilateral S2 [contralateral:  $t(7) = 3.23$ ,  $P < 0.05$ ; ipsilateral:  $t(7) = 3.20$ ,  $P < 0.05$ ], SMA [contralateral:  $t(7) = 4.36$ ,  $P < 0.01$ ; ipsilateral:  $t(7) = 2.96$ ,  $P < 0.05$ ]. The mean BOLD time courses in these regions for both trial types are depicted in Fig. 3. Furthermore, one-sided paired- $t$ -test were applied to examine the statistical significance of the BOLD adaptation effect for the above-mentioned cortical areas at the different time points after stimulus onset (Fig. 4). Interestingly, as early as 3 s after stimulus onset, the BOLD responses in the contralateral S1 and STG revealed significantly stronger activity during diff compared with same trials. The adaptation effect in contralateral SMA and ipsilateral insula reached statistical significance at 4 s, in bilateral S2 and ipsilateral SMA at 5 s, and at last in the contralateral precentral gyrus at 6 s. Note that in the thalamus the difference between the BOLD signal in the same

and diff trials did not reach significance. Their time courses are also displayed in Fig. 3.

DISCUSSION

The current study used an event-related fMRI adaptation paradigm to identify brain regions involved in frequency discrimination of vibrotactile stimuli. Subjects were presented with two vibrotactile stimuli of either the same or different frequency and had to judge which one of the two stimuli vibrated faster. The comparison of the BOLD responses to same and diff trials disclosed response adaptation (i.e., decreased hemodynamic activity during same compared with diff trials) in contralateral S1, STG, precentral gyrus, ipsilateral insula, and bilateral S2 and SMA. The involvement of S1, S2, precentral gyrus, and SMA in vibrotactile processing as identified by the fMRI adaptation paradigm is largely consistent with previous reports based on primate intracortical recordings and human psychophysical experiments (Harris 2006; Harris et al. 2001, 2002; Hernandez et al. 2000; Luna et al. 2005; Romo

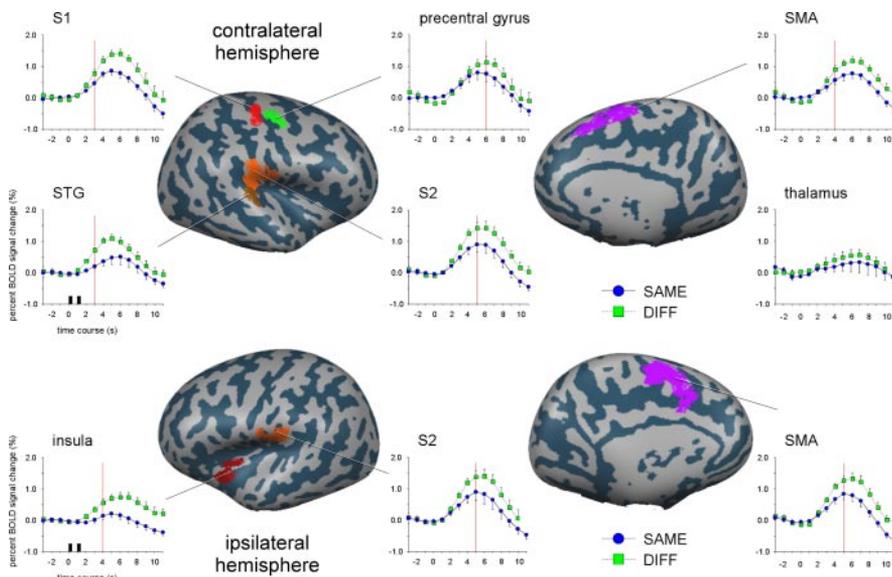


FIG. 3. Mean BOLD time courses ( $\pm$ SE) of thalamus and the cortical areas that showed significant BOLD response adaptation effect. The 2 black rectangles on the time axis indicate the 2 vibrotactile stimuli (duration of each 0.4 s) within a trial. The red vertical line indicates the first time point at which the BOLD response difference between same and different (diff) conditions reached statistical significance ( $P < 0.05$ ).

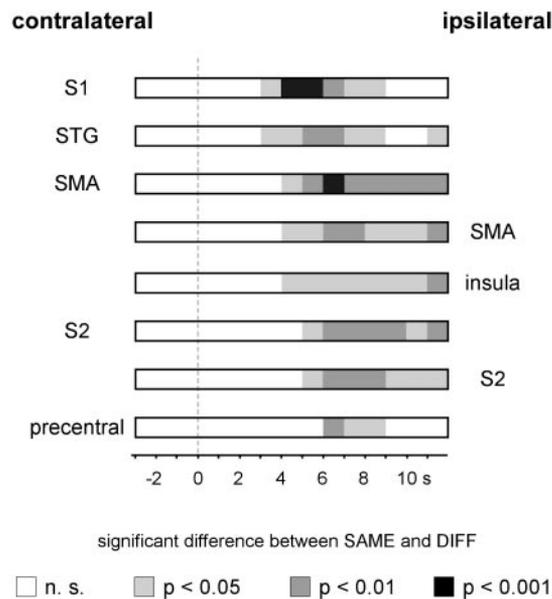


FIG. 4. Temporal pattern of significance of the BOLD response differences between same and diff trials. The dotted vertical line indicates the onset of the 1st stimulus within a trial. Investigating the time course of the BOLD adaptation effect revealed that contralateral primary somatosensory cortex (S1) and superior temporal gyrus (STG) manifested significant response adaptation as early as 3 s after stimulus onset. At 4 s, this response adaptation was seen in the contralateral supplementary motor area (SMA) and the ipsilateral insula, then after 5 s, it was found in secondary somatosensory cortex (S2) bilaterally and ipsilateral SMA. Finally at 6 s the BOLD adaptation reached significance in contralateral precentral gyrus.

and Salinas 2003; Romo et al. 2002a,b, 2004, 2006; Zainos et al. 1997). In addition, our results shed new light on two cortical regions, the contralateral STG and ipsilateral insula, which might also subservise human vibrotactile frequency discrimination. Most interestingly, investigating the time course of the BOLD adaptation effect revealed that contralateral S1 and STG manifested significant response adaptation as early as 3 s after stimulus onset. At 4 s, this response adaptation was seen in the contralateral SMA and the ipsilateral insula, then after 5 s it was found in S2 bilaterally and ipsilateral SMA. Finally at 6 s, the BOLD adaptation was significant in contralateral precentral gyrus. The topographical sequence of the adaptation effect agrees with the flow of information from early sensory areas to higher cognitive areas and could therefore highlight activation of a putative cortical circuitry required in vibrotactile frequency processing and discrimination.

Although the fMRI adaptation paradigm has been widely used especially in the visual modality to identify feature-selective neuronal subpopulations, the underlying neural mechanism of BOLD response adaptation is not yet fully understood (Grill-Spector and Malach 2001; Grill-Spector et al. 2006). Sawamura et al. (2006) have shown that the subsequent response of a neuron would not be influenced if the previous stimulus caused no activation. They found that adaptation only occurs to stimulus-responsive neurons. In our case, when both same and diff vibrotactile stimuli caused similar fMRI responses in certain neurons, one might conclude that these neurons were excited by the stimuli and were invariant to the frequency change. The fMRI adaptation paradigm is thus a good method in exploring the neuronal network sensitive to vibrotactile frequency discrimination.

Nevertheless caution should be taken in generalizing fMRI adaptation results. The response adaptation in some cortical regions might just be due to the adapted input they received from other areas without possessing a stimulus selectivity on their own (Kohn and Movshon 2004; Tolias et al. 2005). This input bias phenomenon also limits the interpretation of our study as we are not able to discern whether the adaptation effect of later activated cortical areas is caused by effect propagation or by their frequency-sensitive neurons. Nevertheless, we were interested in investigating the initiation of the BOLD adaptation phenomenon in vibrotactile stimulation and to delineate the brain areas in which the BOLD response could be propagated during frequency discrimination. Moreover, we did not observe a significant BOLD adaptation in subcortical regions (i.e., thalamus) so that we suggest that the processing and discrimination of vibrotactile frequency starts in S1 and possibly STG simultaneously.

#### Vibrotactile frequency discrimination

The current results suggest that the contralateral S1, STG, precentral gyrus, ipsilateral insula, and bilateral SMA and S2 constitute the cortical network of vibrotactile frequency discrimination in humans. Furthermore, the primary sensory cortex might have dual functions: topographical encoding of the incoming stimulus and short-term storage of this information (Gottlieb et al. 1989; Harris et al. 2002; Pasternak and Greenlee 2005). Our result is well in line with previous studies showing that S1 is closely involved in both cortical operations during a vibrotactile discrimination task (Harris et al. 2002; Romo and Salinas 2003; Romo et al. 2000, 2002a, 2006; Zainos et al. 1997). However, because S1 neurons fire phase-locked after the flutter vibration with no preference of specific frequency (Mountcastle et al. 1990), the frequency selectivity revealed by the fMRI adaptation paradigm remains unclear. Memory storage might be the answer to this phenomenon, which we will discuss in more detail in the following text regarding the interpretation of BOLD adaptation.

Interestingly, we also found contralateral STG to show significantly higher BOLD response to diff in comparison with same stimuli. The STG has been assumed to function as a sensory polymodal integration area (Karnath 2001) and to be an area where audiotactile interaction takes place (Foxe et al. 2002; Fu et al. 2003; Schroeder et al. 2001). Stoeckel and colleagues reported STG activation during a tactile object discrimination task (Stoeckel et al. 2003). An intriguing possibility of the involvement of STG in vibrotactile frequency discrimination was opened by a human MEG study from Caetano and Jousmäki (2006), who demonstrated activations in auditory cortices and subjective perception of a sound by solely stimulating the fingertips with vibrotactile bursts. Our results lend further support to the notion that the conventionally thought pure auditory areas might be involved in the early stages of somatosensory processing. In addition, our finding that STG also showed the earliest significant BOLD response adaptation 3 s after stimulus onset is in accordance with previous electrophysiology studies demonstrating that somatosensory and auditory responses have a very similar temporal profile in the auditory cortices. Both electrical median nerve stimuli as well as auditory stimuli have the same short latency (~12 ms) in reaching the caudomedial region of monkey

auditory association cortex (Schroeder and Foxe 2002; Schroeder et al. 2001), which is supposed to be the homologue of human STG (Foxe et al. 2002). The preceding evidence gives credence to the idea that STG could contribute to the processing and discrimination of vibrotactile frequency. Furthermore, the present study confirmed auditory cortical activation via vibrotactile stimuli with fMRI data.

Our study also demonstrates that bilateral S2 and SMA are part of a neuronal network underlying vibrotactile discrimination. Indeed, monkey S2 neurons have shown activities of encoding and discriminating the two vibrotactile stimuli (Romo et al. 2002b). Moreover, the primate medial premotor cortical neurons seem to participate in the whole process of vibrotactile discrimination as their responses are correlated with various discrimination stages (Hernandez et al. 2002). Furthermore, we also observed significant BOLD adaptation in the contralateral precentral gyrus (primary motor and premotor cortex) in relation to the stimulated hand. This activation is improbable to be the result from the button presses as subjects answered bimanually to the task and the assignment of the buttons to the responses was balanced across subjects. Such contralateral motor cortex activation has been found in other fMRI studies applying unilateral vibrotactile stimulation (Golaszewski et al. 2002, 2006). In addition, several studies using vibrotactile stimulation have also shown insula activation (Burton et al. 1993; Francis et al. 2000; Gelnar et al. 1998; Golaszewski et al. 2006; McGlone et al. 2002). Those studies interpreted this activation due to the role of insula in tactile memory as it receives input from S2 and projects further to the temporal lobe. Thus the response adaptation effect seen in insula and motor cortex could be more than just due to the adapted input from other areas. However, the exact functional role of the BOLD adaptation in the contralateral M1 as well as in the ipsilateral insula requires further evaluation.

#### *Interpretation of BOLD adaptation*

We interpret the present results according to previous fMRI adaptation experiments that uncovered neuronal selectivity for various stimulus features (Kourtzi et al. 2003; Tolia et al. 2001; Tootell et al. 1998), i.e., cortical regions that show a significant BOLD adaptation effect are putatively involved in the processing of the studied stimulus feature—in this study, vibrotactile frequency. This, however, would imply that the detected brain regions might contain frequency-specific neurons. To our knowledge, there has been so far no report on frequency-selective neurons in the human somatosensory system. Nonetheless, two recent electrophysiology studies have demonstrated that rat S1 neurons display vibrissa resonance frequency tuning (Andermann et al. 2004; Neimark et al. 2003). Andermann and colleagues observed a co-existence of “isofrequency columns” with the barrel columns in rat S1. They interpreted their data as an indicator of a vibrotactile information processing system of the vibrissa in parallel to the sound neural representation in the auditory cortex (Andermann et al. 2004). Thus it might be possible that S1 neurons have preferences for certain frequency range partially due to different afferent mechanoreceptors. Nevertheless even this assumption held true; the frequency resolution of these S1 neurons might be too coarse to support the BOLD selective adaptation

in the current study as the frequency difference was of  $\pm 2$  Hz within a pair of vibrotactile stimuli.

Alternatively, sensory memory as an intrinsic neuronal property might also account for the differential BOLD responses to same and diff trials in our study. Repetition suppression, decreased neural activity after repetition of a stimulus with a short interval, has been regarded as a common feature of neurons in prefrontal and temporal visual cortices of either awake behaving (Miller et al. 1996; Rainer et al. 1999) or anesthetized monkeys (Miller et al. 1991a). The repetition suppression effect is thought to be stimulus-specific and to reflect passive or automatic mechanism in visual short-term recognition memory (Baylis and Rolls 1987; Miller and Desimone 1994). Apparently this repetition suppression is not only restricted to the visual modality. Using an oddball design, Ulanovsky and colleagues suggested that the stimulus-specific adaptation elicited in the cat primary auditory neurons by presenting pairs of pure tones (standard/deviant) of various frequency differences seems to reflect auditory sensory memory (Ulanovsky et al. 2003, 2004). Interestingly, in their 50/50% (probability ratio of standard/deviant) control condition, which was comparable to our current design (equal number of same and diff trials), the smaller the frequency difference between the two stimuli, the lower the response magnitude was seen (Fig. 2, Ulanovsky et al. 2004). In particular, given the similarity between their fixed ISI of 736 ms and the current ISI of 600 ms, the BOLD response adaptation effect seems to be analogous to the stimulus-specific adaptation they found. Due to the ubiquity of repetition suppression in the visual (Miller et al. 1996; Rainer et al. 1999) and auditory modality, it is very likely that the reduction of brain response for same but not different frequencies of vibrotactile stimuli in our experiment might rely on the same inherent neuronal mechanism, i.e., intrinsic sensory memory. To corroborate this hypothesis, studies investigating repetition effect on a system level are not sufficient and have to be complemented by experiments on a cellular level. Especially, it is noted that there are frequency-dependent neurons starting from S2 that either increase or decrease their activity monotonically with increasing stimulus frequencies and that also encode frequency differences between two successive stimuli (Romo et al. 2002a, 2003). However, it is unclear how these effects relate to the repetition effect observed on the level of summed mass activity and whether the same or other mechanism underlies the BOLD adaptation effect of different cortical areas. Moreover, neuronal response enhancement after stimulus repetition has also been seen and been suggested to reflect active working memory (Miller and Desimone 1994). Therefore a mixture of parallel neuronal suppression and enhancement due to stimulus repetition and working memory might underlie the current BOLD reduction as the proportion of the neurons showing suppression is usually higher during stimulus repetition in monkey prefrontal and inferior temporal cortex (Miller et al. 1991b, 1993) as well as in S1 (Lee and Whitsel 1992).

#### *Conclusion*

Given the before-mentioned similarities between the vibrotactile and auditory domains, vibrotactile sensory memory could thus lead to the vibrotactile frequency-specific adaptation seen in our data. To further address this question of vibrotactile

frequency-specific adaptation, a parametric design with varying ISIs is needed. It has to be shown whether vibrotactile frequency-specific adaptation persists over a longer period of time as has been shown for the auditory modality (Ulanovsky et al. 2004). Moreover, as revealed by repetitive tactile stimulation, the response magnitude of monkey S1 neurons change with an ISI of 3–5 s and recover fully within 1–2 min in vivo (Lee and Whitsel 1992). Thus to fully understand the cause of the current BOLD adaptation, we have to apply longer ISIs (e.g., 3 s) to investigate the possibility of sensory memory as a mechanism that underlies BOLD adaptation and probably even longer ISIs are needed to underpin the working memory hypothesis.

To summarize, our study used an event-related fMRI adaptation paradigm to investigate the cortical network engaged in vibrotactile discrimination. Along the tactile input pathway, we found that differential BOLD responses to same and different vibrotactile frequency stimulus pairs start to occur as early as 3 s after stimulus onset in S1 and STG simultaneously. The previous finding that vibrotactile stimulation leads to auditory cortical activation could be confirmed using an fMRI approach. The tactile information seems to flow in a cortical circuitry sensitive to vibrotactile frequency change, including the contralateral S1, STG, precentral gyrus, ipsilateral insula and bilateral SMA, S2. Thus the current finding adds information to the human vibrotactile frequency discrimination network and demonstrates that fMRI adaptation paradigm can be effectively applied to study somatosensory perception.

#### ACKNOWLEDGMENTS

We are grateful for technical assistance from J. Dax. Thanks to the anonymous reviewers for invaluable comments.

#### GRANTS

This study was supported by Deutsche Forschungsgemeinschaft Grant SFB 550/C6 and by VW-Stiftung I/80 327 to C. Braun.

#### REFERENCES

- Altmann CF, Deubelius A, Kourtzi Z. Shape saliency modulates contextual processing in the human lateral occipital complex. *J Cogn Neurosci* 16: 794–804, 2004.
- Andermann ML, Ritt J, Neimark MA, Moore CI. Neural correlates of vibrissa resonance; band-pass and somatotopic representation of high-frequency stimuli. *Neuron* 42: 451–463, 2004.
- Baylis GC, Rolls ET. Responses of neurons in the inferior temporal cortex in short term and serial recognition memory tasks. *Exp Brain Res* 65: 614–622, 1987.
- Burton H, Videen TO, Raichle ME. Tactile-vibration-activated foci in insular and parietal-opercular cortex studied with positron emission tomography: mapping the second somatosensory area in humans. *Somatosens Mot Res* 10: 297–308, 1993.
- Caetano G, Jousmaki V. Evidence of vibrotactile input to human auditory cortex. *Neuroimage* 29: 15–28, 2006.
- Fischl B, Sereno MI, Tootell RB, Dale AM. High-resolution intersubject averaging and a coordinate system for the cortical surface. *Hum Brain Mapp* 8: 272–284, 1999.
- Foxe JJ, Wylie GR, Martinez A, Schroeder CE, Javitt DC, Guilfoyle D, Ritter W, Murray MM. Auditory-somatosensory multisensory processing in auditory association cortex: an fMRI study. *J Neurophysiol* 88: 540–543, 2002.
- Francis ST, Kelly EF, Bowtell R, Dunseath WJ, Folger SE, McGlone F. fMRI of the responses to vibratory stimulation of digit tips. *Neuroimage* 11: 188–202, 2000.
- Fu KM, Johnston TA, Shah AS, Arnold L, Smiley J, Hackett TA, Garraghty PE, Schroeder CE. Auditory cortical neurons respond to somatosensory stimulation. *J Neurosci* 23: 7510–7515, 2003.
- Gelnar PA, Krauss BR, Szeverenyi NM, Apkarian AV. Fingertip representation in the human somatosensory cortex: an fMRI study. *Neuroimage* 7: 261–283, 1998.
- Golaszewski SM, Siedentopf CM, Baldauf E, Koppelstaetter F, Eisner W, Unterrainer J, Guendisch GM, Mottaghy FM, Felber SR. Functional magnetic resonance imaging of the human sensorimotor cortex using a novel vibrotactile stimulator. *Neuroimage* 17: 421–430, 2002.
- Golaszewski SM, Siedentopf CM, Koppelstaetter F, Fend M, Ischebeck A, Gonzalez-Felipe V, Haala I, Struhel W, Mottaghy FM, Gallasch E, Felber SR, Gerstenbrand F. Human brain structures related to plantar vibrotactile stimulation: a functional magnetic resonance imaging study. *Neuroimage* 29: 923–929, 2006.
- Gottlieb Y, Vaadia E, Abeles M. Single unit activity in the auditory cortex of a monkey performing a short term memory task. *Exp Brain Res* 74: 139–148, 1989.
- Grill-Spector K, Henson R, Martin A. Repetition and the brain: neural models of stimulus-specific effects. *Trends Cogn Sci* 10: 14–23, 2006.
- Grill-Spector K, Kushnir T, Edelman S, Avidan G, Itzhak Y, Malach R. Differential processing of objects under various viewing conditions in the human lateral occipital complex. *Neuron* 24: 187–203, 1999.
- Grill-Spector K, Malach R. fMRI-adaptation: a tool for studying the functional properties of human cortical neurons. *Acta Psychol* 107: 293–321, 2001.
- Hari R. Evoked potentials elicited by long vibrotactile stimuli in the human EEG. *Pfluegers* 384: 167–170, 1980.
- Harris JA. Psychophysical investigations into cortical encoding of vibrotactile stimuli. *Novartis Found Symp* 270: 238–245, 2006.
- Harris JA, Harris IM, Diamond ME. The topography of tactile working memory. *J Neurosci* 21: 8262–8269, 2001.
- Harris JA, Miniussi C, Harris IM, Diamond ME. Transient storage of a tactile memory trace in primary somatosensory cortex. *J Neurosci* 22: 8720–8725, 2002.
- Hernandez A, Zainos A, Romo R. Neuronal correlates of sensory discrimination in the somatosensory cortex. *Proc Natl Acad Sci USA* 97: 6191–6196, 2000.
- Hernandez A, Zainos A, Romo R. Temporal evolution of a decision-making process in medial prefrontal cortex. *Neuron* 33: 959–972, 2002.
- Karnath HO. New insights into the functions of the superior temporal cortex. *Nat Rev Neurosci* 2: 568–576, 2001.
- Kohn A, Movshon JA. Adaptation changes the direction tuning of macaque MT neurons. *Nat Neurosci* 7: 764–772, 2004.
- Kourtzi Z, Huberle E. Spatiotemporal characteristics of form analysis in the human visual cortex revealed by rapid event-related fMRI adaptation. *Neuroimage* 28: 440–452, 2005.
- Kourtzi Z, Kanwisher N. Representation of perceived object shape by the human lateral occipital complex. *Science* 293: 1506–1509, 2001.
- Kourtzi Z, Tolias AS, Altmann CF, Augath M, Logothetis NK. Integration of local features into global shapes: monkey and human fMRI studies. *Neuron* 37: 333–346, 2003.
- LaMotte RH, Mountcastle VB. Capacities of humans and monkeys to discriminate vibratory stimuli of different frequency and amplitude: a correlation between neural events and psychological measurements. *J Neurophysiol* 38: 539–559, 1975.
- Lee CJ, Whitsel BL. Mechanisms underlying somatosensory cortical dynamics. I. In vivo studies. *Cereb Cortex* 2: 81–106, 1992.
- Luna R, Hernandez A, Brody CD, Romo R. Neural codes for perceptual discrimination in primary somatosensory cortex. *Nat Neurosci* 8: 1210–1219, 2005.
- McGlone F, Kelly EF, Trullsson M, Francis ST, Westling G, Bowtell R. Functional neuroimaging studies of human somatosensory cortex. *Behav Brain Res* 135: 147–158, 2002.
- Miller EK, Desimone R. Parallel neuronal mechanisms for short-term memory. *Science* 263: 520–522, 1994.
- Miller EK, Erickson CA, Desimone R. Neural mechanisms of visual working memory in prefrontal cortex of the macaque. *J Neurosci* 16: 5154–5167, 1996.
- Miller EK, Gochin PM, Gross CG. Habituation-like decrease in the responses of neurons in inferior temporal cortex of the macaque. *Vis Neurosci* 7: 357–362, 1991a.
- Miller EK, Li L, Desimone R. A neural mechanism for working and recognition memory in inferior temporal cortex. *Science* 254: 1377–1379, 1991b.

- Miller EK, Li L, Desimone R.** Activity of neurons in anterior inferior temporal cortex during a short-term memory task. *J Neurosci* 13: 1460–1478, 1993.
- Mountcastle VB, Steinmetz MA, Romo R.** Frequency discrimination in the sense of flutter: psychophysical measurements correlated with postcentral events in behaving monkeys. *J Neurosci* 10: 3032–3044, 1990.
- Mountcastle VB, Talbot WH, Sakata H, Hyvarinen J.** Cortical neuronal mechanisms in flutter-vibration studied in unanesthetized monkeys. Neuronal periodicity and frequency discrimination. *J Neurophysiol* 32: 452–484, 1969.
- Naccache L, Dehaene S.** The priming method: imaging unconscious repetition priming reveals an abstract representation of number in the parietal lobes. *Cereb Cortex* 11: 966–974, 2001.
- Neimark MA, Andermann ML, Hopfield JJ, Moore CI.** Vibrissa resonance as a transduction mechanism for tactile encoding. *J Neurosci* 23: 6499–6509, 2003.
- O'Mara S, Rowe MJ, Tarvin RP.** Neural mechanisms in vibrotactile adaptation. *J Neurophysiol* 59: 607–622, 1988.
- Pasternak T, Greenlee MW.** Working memory in primate sensory systems. *Nat Rev Neurosci* 6: 97–107, 2005.
- Rainer G, Rao SC, Miller EK.** Prospective coding for objects in primate prefrontal cortex. *J Neurosci* 19: 5493–5505, 1999.
- Recanzone GH, Merzenich MM, Schreiner CE.** Changes in the distributed temporal response properties of SI cortical neurons reflect improvements in performance on a temporally based tactile discrimination task. *J Neurophysiol* 67: 1071–1091, 1992.
- Romo R, Hernandez A, Zainos A.** Neuronal correlates of a perceptual decision in ventral premotor cortex. *Neuron* 41: 165–173, 2004.
- Romo R, Hernandez A, Zainos A, Brody C, Salinas E.** Exploring the cortical evidence of a sensory-discrimination process. *Philos Trans R Soc Lond B Biol Sci* 357: 1039–1051, 2002a.
- Romo R, Hernandez A, Zainos A, Brody CD, Lemus L.** Sensing without touching: psychophysical performance based on cortical microstimulation. *Neuron* 26: 273–278, 2000.
- Romo R, Hernandez A, Zainos A, Lemus L, Brody CD.** Neuronal correlates of decision-making in secondary somatosensory cortex. *Nat Neurosci* 5: 1217–1225, 2002b.
- Romo R, Hernandez A, Zainos A, Lemus L, de Lafuente V, Luna R, Nacher V.** Decoding the temporal evolution of a simple perceptual act. *Novartis Found Symp* 270: 170–186, 2006.
- Romo R, Hernandez A, Zainos A, Salinas E.** Somatosensory discrimination based on cortical microstimulation. *Nature* 392: 387–390, 1998.
- Romo R, Hernandez A, Zainos A, Salinas E.** Correlated neuronal discharges that increase coding efficiency during perceptual discrimination. *Neuron* 38: 649–657, 2003.
- Romo R, Salinas E.** Flutter discrimination: neural codes, perception, memory and decision making. *Nat Rev Neurosci* 4: 203–218, 2003.
- Salinas E, Hernandez A, Zainos A, Romo R.** Periodicity and firing rate as candidate neural codes for the frequency of vibrotactile stimuli. *J Neurosci* 20: 5503–5515, 2000.
- Sawamura H, Orban GA, Vogels R.** Selectivity of neuronal adaptation does not match response selectivity: a single-cell study of the fMRI adaptation paradigm. *Neuron* 49: 307–318, 2006.
- Schacter DL, Buckner RL.** Priming and the brain. *Neuron* 20: 185–195, 1998.
- Schroeder CE, Foxe JJ.** The timing and laminar profile of converging inputs to multisensory areas of the macaque neocortex. *Brain Res Cogn Brain Res* 14: 187–198, 2002.
- Schroeder CE, Lindsley RW, Specht C, Marcovici A, Smiley JF, Javitt DC.** Somatosensory input to auditory association cortex in the macaque monkey. *J Neurophysiol* 85: 1322–1327, 2001.
- Stoeckel MC, Weder B, Binkofski F, Buccino G, Shah NJ, Seitz RJ.** A fronto-parietal circuit for tactile object discrimination: an event-related fMRI study. *Neuroimage* 19: 1103–1114, 2003.
- Talbot WH, Darian-Smith I, Kornhuber HH, Mountcastle VB.** 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, 1968.
- Tan H, Wuhle A, Braun C.** Unilaterally applied stimuli in a frequency discrimination task are represented bilaterally in primary somatosensory cortex. *Neurol Clin Neurophysiol* 2004: 1–7, 2004.
- Tobimatsu S, Zhang YM, Kato M.** Steady-state vibration somatosensory evoked potentials: physiological characteristics and tuning function. *Clin Neurophysiol* 110: 1953–1958, 1999.
- Tolias AS, Keliris GA, Smirnakis SM, Logothetis NK.** Neurons in macaque area V4 acquire directional tuning after adaptation to motion stimuli. *Nat Neurosci* 8: 591–593, 2005.
- Tolias AS, Smirnakis SM, Augath MA, Trinath T, Logothetis NK.** Motion processing in the macaque: revisited with functional magnetic resonance imaging. *J Neurosci* 21: 8594–8601, 2001.
- Tootell RB, Hadjikhani NK, Vanduffel W, Liu AK, Mendola JD, Sereno MI, Dale AM.** Functional analysis of primary visual cortex (V1) in humans. *Proc Natl Acad Sci USA* 95: 811–817, 1998.
- Tootell RB, Reppas JB, Dale AM, Look RB, Sereno MI, Malach R, Brady TJ, Rosen BR.** Visual motion aftereffect in human cortical area MT revealed by functional magnetic resonance imaging. *Nature* 375: 139–141, 1995.
- Ulanovsky N, Las L, Farkas D and Nelken I.** Multiple time scales of adaptation in auditory cortex neurons. *J Neurosci* 24: 10440–10453, 2004.
- Ulanovsky N, Las L, Nelken I.** Processing of low-probability sounds by cortical neurons. *Nat Neurosci* 6: 391–398, 2003.
- van Atteveldt N, Formisano E, Goebel R, Blomert L.** Integration of letters and speech sounds in the human brain. *Neuron* 43: 271–282, 2004.
- Vuilleumier P, Henson RN, Driver J, Dolan RJ.** Multiple levels of visual object constancy revealed by event-related fMRI of repetition priming. *Nat Neurosci* 5: 491–499, 2002.
- Whitsel BL, Kelly EF, Quibrera M, Tommerdahl M, Li Y, Favorov OV, Xu M, Metz CB.** Time-dependence of SI RA neuron response to cutaneous flutter stimulation. *Somatosens Mot Res* 20: 45–69, 2003.
- Whitsel BL, Kelly EF, Xu M, Tommerdahl M, Quibrera M.** Frequency-dependent response of SI RA-class neurons to vibrotactile stimulation of the receptive field. *Somatosens Mot Res* 18: 263–285, 2001.
- Zainos A, Merchant H, Hernandez A, Salinas E, Romo R.** Role of primary somatic sensory cortex in the categorization of tactile stimuli: effects of lesions. *Exp Brain Res* 115: 357–360, 1997.