

Somatosensory and auditory change detection system in humans

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Abstract

Quick detection of changes in the sensory environment is very important for survival, resulting in automatic shifts of attention to the event and the facilitation of subsequent processes to execute appropriate behaviors. The abrupt onset or offset of a sensory stimulus should also activate the neural network detecting changes. In the first study, to test this hypothesis, we compared cortical on- and off-responses using somatosensory evoked potentials (SEPs) elicited by a train of electrical pulses delivered to the right hand in eight healthy volunteers. SEPs were recorded from 15 electrodes on the scalp at three different interstimulus intervals (ISIs, 50, 20, and 10 ms) under two sets of conditions (attended and unattended). Both the onset and offset of stimulation evoked two similar components, P100 and N140, in the attended and unattended conditions. The latency of P100 and N140 in response to stimulus onset did not differ among the three ISIs, while the latency of both components in response to stimulus offset was significantly longer for the longer ISI; that is, detection of the cessation of the stimulation was based on short-term memory of the stimulus frequency. The present results supported a cortical

network triggered by both the onset and offset of sensory stimulation. In this network, the change is automatically detected using a memory trace by comparing the abrupt event (on or off) with the preceding condition (silent or repetitive stimuli).

In the second study, we recorded cortical activities in response to the onset and offset of a train of electrical pulses applied to the right hand in eleven healthy volunteers by use of magnetoencephalography (MEG) to clarify temporal and spatial profiles of the somatosensory on- and off-cortical responses. Results showed that a region around the upper bank of the sylvian fissure of both hemispheres responded to the onset and offset of the stimulus, while the activity in the primary somatosensory cortex (SI) of the hemisphere contralateral to the stimulation was clear only for the onset response. The SI activity consisted of two components suggesting that two distinct populations of neurons in SI were involved in processing a train of pulses. The location of the source of activity in the contralateral para-sylvian region (cPara) differed significantly between the on- and off-response, while that of the activity in the ipsilateral para-sylvian region (iPara) did not. The differences in location of the cPara activity might be

caused by the overlapping of several cortical activities in response to each stimulus and stimulus event (on and off events), while the iPara activity might reflect purely the event-related response. Moreover, some subjects had clear iPara activity without cPara activity especially in the off-response, suggesting the iPara activity to be independent of the cPara activity. We consider that activities in the parasyylvian region are involved in the detection of changes at the body's surface.

In the third study, we recorded cortical activities in response to the onset and offset of a pure tone of long duration (LONG) and a train of brief pulses of a pure tone with an interstimulus interval of 50 ms (ISI-50 ms) or 100 ms (ISI-100 ms) by use of MEG in eleven healthy volunteers to clarify temporal and spatial profiles of the auditory on- and off-cortical response. Results showed that a region around the superior temporal gyrus (STG) of both hemispheres responded to both the onset and offset of the stimulus. The location of the source responsible for the main activity (N1m) was not significantly different between the on- and off-responses for any of the three tones. The peak latency of on-N1m was similar under the three conditions, while the peak latency of off-N1m was precisely determined by

the ISI, which suggested that off-N1m is based on short-term memory of the stimulus frequency. In addition, there was a positive correlation of the amplitude of N1m between the on- and off-responses among the subjects. The present results suggested that auditory on-N1m and off-N1m have similar physiological significance involved in responding to abrupt changes.

General Introduction

One of the most important functions of sensory processing in animals is to quickly detect and respond to changes in the surrounding environment. Automatic shifts of attention to an event lead to the facilitation of subsequent processes to execute appropriate behavior. In humans, a cortical network sensitive to sensory changes is known to exist (Downar et al., 2000).

Although previous studies used changes in stimulation to investigate the cortical network sensitive to sensory changes, we used the off-response elicited by the change-event not by the second stimulus following a physically different first stimulus. If a mechanism to detect changes is

present, the off-event as well as the on-event should be detected as a sensory change and cortical activations should be observed. In fact, cortical off-responses have been observed in the auditory (Hari et al., 1987; Noda et al., 1998; Pantev et al., 1996; Wakai et al., 2007), visual (Crevits et al., 1982) and somatosensory (Downar et al., 2003; Spackman et al., 2006) systems as well as cortical on-responses. Therefore, there may be similar cortical mechanisms for detecting changes among all the sensory modalities. However, the relationship between the on- and off-responses for detecting sensory changes has been unclear.

In the present study, we recorded cortical activities in response to the onset and offset of the stimulation by use of electroencephalography (EEG) and MEG to clarify temporal and spatial profiles of the on- and off-responses between the somatosensory and auditory modalities. The results would reveal a similarity between the on- and off-responses for the detecting sensory changes.

Experiment 1: SEPs study

The rapid detection of changes at the body surface or in the environment is very important for survival. In humans, the presence of a brain network sensitive to sensory changes has been demonstrated (Downar et al., 2000). Activation of this network is expected to unconsciously shift attention to the environmental event and facilitate subsequent processes leading to the execution of appropriate behaviors. In view of the quick detection of changes, the abrupt appearance or disappearance of stimuli should also drive the detection network. For example, a quiet sound during complete silence as well as an abrupt cessation of loud singing by birds draws great attention. We hypothesized that the abrupt onset and offset of a sensory stimulus activate a similar cortical network to that involved in the automatic detection of changes in the sensory environment by comparing the abrupt event (on or off) with the preceding condition (silent or repetitive stimuli). Although a few studies have investigated cortical off-responses using functional magnetic resonance imaging (fMRI), (Downar et al., 2003), EEG (Spackman et al., 2006), and MEG (Hari et al., 1987; Noda et al., 1998; Pantev et al., 1996; Wakai et al., 2007), this issue

has not been examined.

To test the hypothesis, we compared cortical on- and off-responses using SEPs. We also compared the responses between attended and unattended conditions to test the automatic nature of the on- and off-responses since an important aspect of the neural network detecting change is the automatic capturing of attention. The somatosensory modality was employed because it is very easy to control the variables (intensity, duration, pulse frequency and inter-trial interval) and very precise in terms of timing of the onset and offset of the stimulation.

Methods

Subjects

The experiments were performed on eight (two female and six male) healthy right-handed volunteers (24-42 years). The study was approved in advanced by the Ethics Committee of the National Institute for Physiological Sciences, Okazaki, Japan, and written consent was obtained from all subjects.

Recordings

EEG signals were recorded using 15 scalp electrodes placed at F3/F4, F7/F8, C3/C4, T3/T4, T5/T6, P3/P4, Fz, Cz, and Pz according to the 10-20 system. The linked earlobes were used as a reference. Electro-oculograms (EOGs) were recorded using a pair of electrodes placed on the supra- and infra-orbit of the right eye for the automatic rejection of trials with blink artifacts. Electrode impedance was kept below 5 k Ω . EEG signals were recorded with a bandpass filter of 0.1-100 Hz at a sampling rate of 2000 Hz, and then digitally filtered with a 70-Hz low-pass filter. The window of analysis was from 100 ms before to 400 ms after the stimulus onset and offset. The 100-ms period before the trigger point was used as the DC baseline.

Stimuli

SEPs were elicited with a train of current-constant square wave pulses (pulse duration, 0.5 ms) for 1-3 s delivered to the dorsum of the right hand between the first and second metacarpal bones using a bipolar felt tip electrode. The intensity of the stimulus was 1.5 times the sensory threshold.

There were three ISIs 50, 20, and 10 ms. The inter-trial interval (ITI) was 10-12 s.

Procedures

Experiment 1 (attended task)

At each ISI, 24 artifact-free responses were recorded in three separate blocks (eight responses in each block); therefore, there were nine blocks (3 ISIs x 3 blocks). The order of the nine blocks was randomized among subjects. The interval between blocks was about 2 min. Subjects were instructed to pay attention to the stimulus and not to blink from the stimulus onset to 1 s after the stimulus offset. The mean intensity of the stimulus was 2.6 ± 0.5 mA.

Experiment 2 (unattended task)

Experiment 2 was performed about two weeks after Experiment 1. The procedures were identical to those of Experiment 1 except that subjects watched a silent movie throughout the experiment. Since the likelihood of trials with artifacts was higher than in Experiment 1, the experiment was

lengthened slightly (on average, 35 min instead of 25 min). The mean intensity of the stimulus was 3.1 ± 0.5 mA.

Analysis

Averaged waveforms at three ISIs (50, 20, and 10 ms) were obtained for each subject in Experiment 1 and Experiment 2. There were two main components, P100 and N140, common to the three ISIs and two task conditions. These components were analyzed in the present study. The peak latency of P100 and N140 for the onset response was determined during a latency period of 70-120 ms and 120-180 ms, respectively, at Cz. The timing of the offset response was expressed as latency relative to the last pulse of the train stimulus. Since we used a train of electrical pulses at three different frequencies, the latency of the cortical off-response should be determined differently according to the train's frequency. In the case of 20 pulses at 50-ms intervals, for example (a 20Hz train for 1 second), the offset should be determined at the latency of the 21st pulse, 50 ms later than the last pulse. We referred to the offset-determining latency point as the 'offset-discriminating point' (ODP). In addition to the originally

measured latency, the ODP-based response latency was analyzed for the offset response. The peak latency of P100 and N140 for the offset response was determined during slightly (10-100 ms according to the ISI) later latency periods than used for the on-response.

The similarity of the field distribution pattern at the peak of the two components between the on- and off-responses and between Experiment 1 and Experiment 2 (attended vs non-attended) was assessed by determining the correlation coefficient, r (Inui et al., 2006a for the detailed method). Since the offset of the three different trains of pulses evoked very similar waveforms with a difference in latency depending on the ODP, as expected, the waveforms of the off-response for all three ISIs were averaged by adjusting the latency of each waveform so that the ODP of each condition matched on the time axis. To assess the similarity of the distribution, we used the ODP-corrected grand-averaged waveform for the off-response in each subject.

Results

On- and off-responses in Experiment 1 (attended task)

Figure 1 shows on- and off-responses at Cz in a single trial involving 200 electrical pluses at 100 Hz for 2 s in a representative subject. While trains of pluses for 2 s were presented, the onset of the stimulation evoked two clear components, P100 and N140. The P100 component showed positivity with the maximal amplitude at Cz at around 90 ms after stimulus onset. N140 was negative with the maximal amplitude at Cz peaking at around 140 ms. The mean latency of these two components for each ISI across subjects is listed in Table 1. The latency of P100 or N140 did not differ among the three ISIs (ANOVA, $p = 0.97$ for P100 and $p = 0.09$ for N140). In addition to these components, slow positivity was elicited at Cz and Pz.

The offset of the stimulation evoked two clear components similar to P100 and N140 of the on-response at each ISI. Unlike for the on-response, however, the latency of both components in response to the stimulus offset differed significantly ($F_{(2,14)} = 54.9$, $p < 0.0001$ for P100 and $F_{(2,14)} = 29.8$, $p < 0.0001$ for N140) among the three ISIs. The latency of both P100 and

N140 was shortest at 10 ms followed by 20 ms and 50 ms (Table 1). For instruction purposes, the grand-averaged waveforms across all subjects are depicted in Figure 2. The mean difference of the latency of P100 between on- and off-responses at 50 ms, 20 ms and 10 ms was 74 ± 14 ms, 34 ± 12 ms, and 29 ± 16 ms, respectively. The difference in the latency of N140 between on- and off-responses was 71 ± 17 ms, 44 ± 21 ms, and 28 ± 18 ms, respectively; that is, the entire waveform of the off-response was shifted on the time axis according to the ODP.

Based on these findings, we averaged the off-response at the three ISIs by correcting the latency using the ODP, and compared the field distribution across all electrodes between the on- and off-responses at the P100 and N140 latencies in each subject. The mean r value was 0.70 ± 0.15 for P100 and 0.63 ± 0.17 for N140. The correlation of P100 and N140 was statistically significant ($p < 0.05$) in six and seven of eight subjects, respectively.

On- and off-responses in Experiment 2 (unattended task)

In Experiment 2, we tested whether these off-responses could be

evoked without cognitive tasks. Both the onset and offset of the stimulus evoked waveforms very similar to those in Experiment 1, except that there was no slow positive component. As in Experiment 1, the peak latency of P100 and N140 for the off-response differed significantly ($F_{(2,14)} = 101.9$ $p < 0.0001$ for P100 and $F_{(2,14)} = 32.7$ $p < 0.0001$ for N140) among the three ISIs, while the peak latency for the on-response did not ($p = 0.56$ for P100 and $p = 0.16$ for N140). The mean difference in the peak latency of P100 between the on- and off-responses for 50 ms, 20 ms, and 10 ms was 66 ± 15 ms, 34 ± 9 ms, and 27 ± 9 ms, respectively (Table 1). When the field distribution pattern was compared between on- and off-responses, the mean r value was 0.66 ± 0.14 for P100 and 0.62 ± 0.13 for N140. The correlation of P100 and N140 was statistically significant ($p < 0.05$) in five and four of eight subjects, respectively (Fig. 3). When the field distribution of the off-response was compared between Experiment 1 and 2, the mean r value was 0.90 ± 0.06 for P100 and was 0.85 ± 0.10 for N140. The correlation of P100 and N140 was statistically significant ($p < 0.05$) in all subjects. The mean slope of the regression line (off/on) was 0.75 ± 0.24 for P100 and 0.65 ± 0.09 for N140.

Discussion

In the present study, we tested using SEPs in humans whether the abrupt onset and offset of sensory stimulation activated a similar cortical network to that involved in the automatic detection of changes in the sensory environment. The results supported the hypothesis, at least in part, showing that 1) both the onset and offset of a train of electrical stimulation elicited two components, P100 and N140, with similar timing and topography, 2) the off-response was similar between attended and unattended conditions with respect to timing and topography, and 3) the latency of these two components of the off-response was determined precisely using the offset-discriminating point (that is, the latency of the last pulse plus the interstimulus interval).

Memory-based off-response

Since the main components of the on-response, P100 and N140, in this study appeared at a similar latency irrespective of the stimulus frequency, these components could be considered mainly as a train-onset response. In addition, responses to each pulse might also contribute to shape these

components to some degree. On the other hand, P100 and N140 components of the off-response were triggered by the off event, and therefore a pure train-off response without an integrated response in the projecting area. Therefore, both the off-response and main part of the on-response in this study came from the stimulus event (on and off), but not from the summation of neuronal firings in response to the on and off of each pulse (Fig. 1). Furthermore, the latency of P100 and N140 in response to the stimulus offset depended precisely on the ODP at three ISIs, suggesting clearly that the off-response in this study was not a result of off-firings of SI neurons in response to each pulse. The dependence of the latency of P100 and N140 of the off-response on the ODP was similarly observed in attended and non-attended conditions (Fig. 2b,c); therefore, these findings also suggest that the off-response in this study was a memory-based automatic cortical response.

Recently, studies using oddball paradigms reported mismatch negativity (MMN), an automatic memory-based process for the detection of changes (Näätänen et al., 1989, 2005). Näätänen and Picton (1987) proposed two types of auditory change responses, the type 1 response to a change in level

(or physical energy) and the type 2 response to a change in a stimulus feature without a change in level (e.g. change in pitch or location). They stated that the “true” N1 components (type 1) are largely determined by the physical characteristics of the stimulus and by the general state of the subjects, while other components in the latency region of the N1 (type 2) are related more to memory and cognition than to stimulus and state.

The off-response in the present study might correspond to the type 1 change response in the auditory system when we consider the cessation of repetitive electrical stimulation as a simple change in level (from presence to absence) without any change in feature. However, if the abrupt cessation of stimulation is taken as an absence of the expected stimulus (that is, the missing stimulus at ODP), it means an abrupt break of the rhythmic feature of stimulation; therefore, it appears that the off event in this study could elicit a type 2 response. The present results on ODP support this notion.

In the auditory system, the latency of MMN is dependent on the magnitude of stimulus change (for review, see Näätänen et al., 2005). For example, the MMN peaked about 200 ms with very small frequency change while at 100-150 ms with wide frequency changes. If we apply this

rule to our off-response, its latency is expected to be the shortest since the magnitude of the stimulus change (off) in this study was large as compared to the subtle change in the sound frequency; therefore, we consider that the present results are not incongruent with the idea that P100 or N140 of the off-response is a MMN-like component. In previous studies on somatosensory MMN using a standard oddball paradigm, an MMN-like component was found at 100-200 ms (for example, Kekoni et al. 1997; Shinozaki et al. 1998). The MMN-like components elicited by somatosensory stimuli are also considered to represent the automatic detection of somatosensory change that relies on sensory memory trace (Akatsuka et al., 2005, 2007); however, the present results are insufficient to draw a definite conclusion on the relationship between the off-response and MMN.

Comparison of on- and off-responses

In this study, the common components of the on- and off-responses were P100 and N140, which are known to be elicited following tactile stimulation of the hand (Desmedt and Robertson, 1977; Desmedt and

Tomberg, 1989). In a recent EEG study, Spackman et al. (2006) investigated somatosensory off-responses using 70 Hz vibratory stimulation and found off-N130 as a somatosensory off-response. Their off-N130 seems to correspond to N140 in the present study. Both P100 and N140 are known to be sensitive to the ISI and subject's attentional state; that is, both P100 and N140 increased in amplitude with an increase in the ISI (Kekoni et al., 1996, 1997; Tanaka et al., 2008) and with the performance of cognitively demanding tasks (Kida et al., 2004, 2006b). Some researchers have ascribed this to the involvement of these components in shifts of attention toward sudden sensory inputs against a 'silent' background (Kekoni et al., 1996, 1997; Kida et al., 2004, 2006b). For example, Kida et al. (2004, 2006b) compared P100 and N140 between oddball and deviant alone conditions, and found that the amplitude of both components was larger for the latter condition. They concluded that both P100 and N140 are related to capturing attention for temporally infrequent (sudden) sensory inputs, which is consistent with our conclusion that at least part of the P100 and N140 components of the on-response represents an automatic cortical response to somatosensory changes. Furthermore, the

similarity of these components between on- and off-responses is congruent with the notion that abrupt onset as well as cessation of a sensory stimulus results in an orienting response.

In an fMRI-based study, Downar et al. (2003) recorded on- and off-responses to transcutaneous electrical stimulation of 60 s to the right wrist. They found common transient activations triggered by both the onset and offset of the stimulation in a wide area of the cerebral cortex, such as the temporo-parietal junction, anterior cingulate cortex, and inferior frontal gyrus. Although the present study could not reveal the neural origins of P100 and N140, these cortical areas are likely candidates since they are known to be involved in a cortical network sensitive to sensory changes (Downar et al., 2000), stimulus salience (Downar et al., 2002), and oddball paradigms (McCarthy et al., 1997). In our recent source modeling study of the on-response (Tanaka et al., 2008), the main generator was estimated to be located in the parasyllvian region for P100 and in the anterior cingulate cortex for N140. In addition, the large slow positive component following N140 was evoked only in the attended condition (Experiment 1). This component may correspond to the sustained response of the somatosensory

and auditory systems in previous studies, which is known to be modulated by attention. In an MEG study, Forss et al. (2001) demonstrated sustained activation in SII in response to 8-12 Hz median nerve stimulation, which lasted for several 100 ms after the last stimulus in the train. They suggested stimulus integration in SII, which could contribute to the memory mechanism of the off-response in this study.

For the common network between on- and off-responses, we should also consider the contribution of SI activities. Although the train stimulation of the present study is expected to evoke early SI components (e.g. 20/35 ms) or lateralized stimulation frequency sharp responses (MEG studies, for example, Forss et al., 2001), such a response was not observed in any subject. This is probably due to that the present study used transcutaneous stimulation and EEG. In general, early components are difficult to clearly evoke by transcutaneous stimulation as compared to nerve stimulation, and MEG is more sensitive to early activities than EEG; therefore, the cortical areas responsible for the off-response as well as the possibility of the SI contribution should be clarified in future studies, such as by using MEG.

Comparison of the auditory and somatosensory off-response

In previous studies on auditory off-responses using EEG and MEG, it has been shown that the offset of a tone stimulus evoked a clear component similar to N100 of the on-response (Hari et al., 1987; Hillyard and Picton, 1978; Noda et al., 1998; Pantev et al., 1996; Wakai et al., 2007) and the amplitude of the response increased with an increase of the duration of the tone presentation (Hillyard and Picton, 1978). The latencies of the on-N100 and off-N100 components were not significantly different (Hari et al., 1987; Hillyard and Picton, 1978; Noda et al., 1998; Pantev et al., 1996) and the location of the estimated dipole was not significantly different (Hari et al., 1987; Pantev et al., 1996) or was very similar between the two (Noda et al., 1998); therefore, off-N100 is considered to represent a response to abrupt auditory changes (Hari et al., 1987; Pantev et al., 1996).

The similar latency of on-N100 and off-N100 in the auditory study is different from the present results. This is probably because a continuous tone was used in these studies while a train of pulses was used in the present study. When the dependence of the latency of the off-response on ODP is taken into consideration, the results of previous auditory studies

and our results appear not so different; however, the auditory off-response was slightly shorter than the on-response by 5-13 ms (Hari et al., 1987; Hillyard and Picton, 1978; Noda et al., 1998; Pantev et al., 1996), while the somatosensory off-response was slightly longer than the on-response by 14-24 ms. This discrepancy may reflect the difference between somatosensory and auditory modalities. The precise mechanisms of such a discrepancy remain to be solved. Although the automatic nature of the off-response has not been investigated in the auditory system, Wakai et al. (2007) recently reported that auditory off-responses could be elicited in infants without clear on-responses, implying that off-responses are automatic cortical responses also in the auditory modality.

Based on the present results, we concluded that at least some of the on- and off-responses in the somatosensory system arises from a common cortical network sensitive to sensory changes. In this network, the change is automatically detected by comparing the abrupt event (on or off) with the preceding condition (silent or repetitive stimuli). Such a network is expected to be present in all sensory modalities.

Experiment 2: Somatosensory evoked magnetic fields (SEFs) study

In the first study, both the onset and offset of stimulation elicited two components, P100 and N140, with a similar timing and topography (Yamashiro et al., 2008). Moreover, the latency of these two components of the off-response was determined precisely using the ODP. These results suggested that a cortical network for detecting changes was automatically activated by comparing the abrupt event (on or off) with the preceding condition (silent or repetitive stimuli) using a memory trace.

The time course of the on- and off-responses has been described in scalp EEG (Spackman et al., 2006; Yamashiro et al., 2008) and subdural (n=1) (Spackman et al., 2006) recordings and the locations of the responses have been shown in imaging studies (Downar et al., 2003). A new approach would be the MEG dipole method, combining good spatial and excellent temporal resolution. Comparison of the time course of each cortical activation between the on- and off-responses was the main purpose of the present study.

Methods

Subjects

The experiments were performed on eleven (three female and eight male) healthy right-handed volunteers (25-45 years). The study was approved in advanced by the Ethics Committee of the National Institute for Physiological Sciences, Okazaki, Japan, and written consent was obtained from all the subjects.

Electrical Stimulation

SEFs were elicited with a train of current-constant square wave pulses (pulse duration, 0.5 ms) applied to the dorsum of the right hand between the first and second metacarpal bones using a felt-tip bipolar electrode. The ISI was 20 ms (50 Hz) and the stimulus duration was 3 s. The intensity of the stimulus was 1.5 times the sensory threshold (2.3 ± 0.8 mA). The ITI was 10 s.

MEG recording and analysis

The experiments were carried out in a magnetically-shielded room.

Subjects were instructed to watch a silent movie throughout the experiment. SEFs were recorded with a helmet-shaped 306-channel MEG system (Vector-view. ELEKTA Neuromag. Helsinki, Finland), which comprised 102 identical triple sensor elements. Each sensor element consisted of two orthogonal planar gradiometers and one magnetometer coupled to a multi-superconducting quantum interference device (SQUID) and thus provided 3 independent measurements of the magnetic fields. In this study, we analyzed MEG signals recorded from 204 planar-type gradiometers. These planar gradiometers are powerful enough to detect the largest signal just over local cerebral sources. The signals were recorded with a bandpass of 0.1-100 Hz and digitized at 1000 Hz. The period of analysis for both the on- and off-responses was 500 ms including a prestimulus period of 100 ms that was used as the baseline. The off-response was triggered by the last pulse in the train. Trials with noise (> 2700 fT / cm) were rejected from the analysis automatically. For both the on- and off-responses, 150 artifact-free trials were recorded.

To identify sources of the evoked activities, the equivalent current dipole (ECD), which best explains the measured data, was computed by

using a least-squares search. A subset of 14-20 channels including the local signal maxima was used for the estimation of ECDs. These calculations gave the three-dimensional (3D) location, orientation, and strength of the ECD in a spherical conductor model, which was based on each subject's MRI, to show the location of a source. The goodness-of-fit value of an ECD was calculated to indicate in percentage terms how much the dipole accounts for the measured field variance. Model adequacy was assessed by examining percent variance (Hari et al., 1988). Only ECDs explaining more than 80% of the field variance for selected periods of time were used for further analysis. The period of analysis was extended to the entire time period and all channels were taken into account when computing a time-varying multi-dipole model. The strength of the previously found ECDs was allowed to change while locations and orientations were kept fixed. The data acquisition and analysis followed Hämäläinen et al. (1993). MRI scans were obtained from all subjects with a 3.0-T Siemens Allegra scanner. T1-weighted coronal, axial, and sagittal image slices obtained every 1.5 mm were used for rendering the 3D reconstruction of the brain's surface. Prior to the recording, a current was fed to four head position

indicator (HPI) coils placed at known sites to obtain the exact location of the head with respect to the sensor and the resulting magnetic fields were measured with the magnetometer, which allowed for aligning of the individual head coordinate systems with the magnetometer coordinate system. The four HPI coils attached to the subject's head were measured with respect to the three anatomical landmarks using a 3D digitizer to allow alignment of the MEG and MRI. The x-axis was fixed with the preauricular points, the positive direction being to the right. The positive y-axis passed through the nasion and the z-axis thus pointed upward.

The peak latency of each cortical source activity was compared between the on- and off-responses with a paired-t test. The statistical significance of the location of a source was assessed by a discriminant analysis using the x, y, and z coordinates as variables.

Results

Source location

Figure 4 shows the on- and off-responses in a representative subject. In the on-response, a clear and consistent component was evoked in three

cortical areas (Fig. 4A). By the ECD analysis, dipoles responsible for these responses were estimated to be located in the postcentral gyrus of the contralateral hemisphere (cSI) and the parasyylvian region of both hemispheres around the upper bank of the sylvian fissure. In this paper, we refer to the dipoles in the parasyylvian region as Para. The mean location of each source is shown in Table 2. In the off-response, two components were evoked in the temporo-parietal region of both sides (Fig. 4B) in eight out of eleven subjects. Like the on-response, dipoles responsible for the off-response were estimated to lie in and around the sylvian fissure. However as shown in Fig. 5, the source of cPara was located more lateral (5.7mm), anterior (10.1mm), and inferior (9.5mm) in the on-response than the off-response (discriminant analysis, $P = 0.003$). On the other hand, the source of iPara did not differ significantly between the on- and off-responses. ($P = 0.45$)

Time course of the cortical activity

Figure 6 shows the time course of each activity of the on- and off-responses. Table 3 shows the mean peak latency and amplitude of each

activity. In all subjects, the cSI activity had two distinct components. One component was a train of small sharp transients that responded faithfully to each pulse and the other was a larger long-lasting activity.

In contrast to the cSI activity, the sources in the bilateral Para were activated by both the onset and offset of the stimulus. The time course of the strength of these Para activities was similar to that of the large component of the cSI activity. A two-way ANOVA (event x hemisphere) indicated both event (on or off) and hemisphere to be significant factors determining the peak latency of the Para activities. As for the difference between the on- and off-responses, the mean peak latency of cPara and iPara of the on-response was significantly earlier than that of cPara and iPara of the off-response (cPara, 19.3 ms; iPara, 21.8 ms). As for the difference in latency between hemispheres, the peak latency of cPara was significantly earlier than that of iPara (7.6 ms, $P = 0.025$) in the on-response and tended to be earlier in the off-response (10.3 ms, $P = 0.098$). These results show that the time sequence of the Para activities was similar between the on- and off-responses except for the time delay for the latter.

Discussion

The present study investigated the location and time course of the cortical activities in response to the onset and offset of a tactile stimulus in detail using MEG. The onset of the stimulus activated cSI, cPara and iPara, while the offset activated only cPara and iPara. Main findings of the present study are as follows. (i) The cSI activity in response to the stimulus onset was composed of two different components. One component showed a primary response-like activation pattern responding to each pulse faithfully (stimulus-related) and the other was a single activity of long duration (event-related). (ii) Although both the onset and offset of the stimulus activated a cortical region(s) around the upper bank of the sylvian fissure of the contralateral hemisphere, the location of the source was significantly different between the on- and off response. (iii) The onset and offset of the stimulus activated a similar cortical area in the ipsilateral parasyylvian region. (iv) The time course of the activity in cPara and iPara was similar between the on- and off- responses except for a time delay of about 20 ms for the latter.

The activity of cSI of the on- and off-responses

SI is known to play an important role in the discriminative aspects of tactile processing such as determination of the intensity, location and type of sensory input. The sharp cSI activity responding to each pulse in the present study seems to be involved in such a function. Similar responses have been reported in previous SEF studies in humans (Forss et al., 2001; Hamada et al., 2002; Hoshiyama and Kakigi, 2003; Nangini et al., 2006; Wikstrom et al., 1996). For example, Forss et al. (2001) found that the response of cSI to each stimulus was sharp up to 12 Hz and suggested that SI as a primary projection area may respond strictly to each stimulus to produce temporally and spatially accurate information about the stimuli. Neurons in SI that faithfully respond to high frequency tactile stimulation are well studied in animals (e.g. Ahissar et al., 2000).

The later and larger cSI activity peaking at 69-137ms has only one component of long duration and seems to be related to the on-event. Some MEG studies (Inui et al., 2003a; Mauguiere et al., 1997a) reported a similar late cSI activity following a single electrical pulse. Mauguiere et al. (1997a) suggested the long-lasting activities to be compatible with a

top-down control mediated via cortico-cortical backward projections. The late cSI activity would reflect more advanced processes than the early cSI activity. In an animal study (Derdikman et al., 2006), different activation mechanisms have been demonstrated for the sharp activity and slow activity in SI.

Although activity in cSI triggered by the offset of stimulation has been demonstrated in humans using subdural recordings (Spackman et al., 2006, n=1) and fMRI (Downar et al., 2003), the present study failed to find such activity for the off-response (Fig 4B). In addition to these studies in humans, electrophysiological studies in animals have also demonstrated SI neurons responding to changes (Mountcastle, 1957; Sinclair and Burton, 1991) or the offset (Sur et al., 1984) of somatosensory stimulation. We consider the failure of the present study to detect the off-SI activity to be due to the insensitivity of MEG to detect a current radial to the brain's surface such as that originating from area 1 or 3a. The method used in the present study to estimate dipoles should also be considered. Since the cSI activity for the off-response was very weak as compared with that for the on-response (Fig. 4B), it could be masked by the main activation in the

parasyylvian region under the procedures of the present study. The off-response in SI might have been seen if more trials were used in the averaging.

Activities in the parasyylvian region

The location and response latency of the cPara activity in this study were compatible with those of previous studies (for review, see Hari and Forss, 1999) using a single stimulus. This finding suggests a function of cPara as a second or higher level processing area. In support of this notion, previous studies suggested that this region is involved in higher order functions, such as attention (Burton et al., 1993; Hari et al., 1990; Mauguiere et al., 1997a, b; Mima et al., 1998), tactile texture discrimination (Ledberg et al., 1995), sensorimotor integration (Inoue et al., 2002; Kida et al., 2006a; Lin and Forss, 2002; Wasaka et al., 2007), and the integration of nociceptive and nonnociceptive inputs (Frot et al., 2001; Hari and Forss, 1999; Inui et al., 2003a, 2004; Ploner et al., 1999). In addition, the present finding that the bilateral Para responded to not only the onset but also the offset of the stimulus, suggested that Para responded to the

event (on and off) irrespective of the nature of the stimulus itself. This notion is consistent with previous fMRI studies showing that sudden changes in continuous tactile stimuli activate this cortical area (Downar et al., 2000, 2003).

The peak latency of cPara and iPara activities was significantly longer by about 20 ms for the off-response than that of the activities of the on-response. This result is consistent with our previous study (Yamashiro et al., 2008), which showed that the latency of P100 and N140 of the off-response was determined by the ODP and always longer than that of the on-response. Intracerebral recording studies (Allison et al., 1989, 1992; Frot et al., 2001; Frot and Mauguiere, 1999) reported that the P100 component originated in the perisylvian region. Therefore, the cPara activity in the present study would have helped to shape P100 in our previous study. Since ODP is the timing at which the brain theoretically knows that the train of pulses stops, the latency delay of the Para activities of the off-response compared to those of the on-response also supports the idea that this cortical region is involved in the detection of changes based on short-term memory.

The difference in the location of the contralateral Para between the on- and off-responses

In previous neuroanatomical studies (Disbrow et al., 2000; Eickhoff et al., 2007), at least three subregions within the parietal operculum have been demonstrated. Disbrow et al. (2000) showed that the most consistent locus of activation for the stimulation of the body was the large central area, SII and parietal ventral area (PV). They also showed two additional areas, one rostral and one caudal to this large central area. In the present study, the cPara dipole of the on-response in six of eight subjects appears to correspond to SII/PV or the rostral area among the subregions in the study by Disbrow et al. but the cPara dipole of the on-response in two subjects was slightly superior to the central region. On the other hand, the iPara dipole of the on-response and bilateral Para dipole of the off-response seem to correspond to SII/PV or the caudal area except in two subjects. This might suggest that on- and off-responses are processed in different cortical areas.

Consequently, statistical data showed a significant difference in where the source of activity in cPara was located between the on- and

off-response. That is, the cPara dipole of the on-response was located more anterior, lateral, and inferior than that of the off-response. Since tactile stimuli activate multiple sources in the parasyylvian region in MEG (Disbrow et al., 2001; Inui et al., 2003a), PET (Burton et al., 1993, 1997) and fMRI (Ferretti et al., 2007; McGlone et al., 2002; Torquati et al., 2005) studies, we considered the possibility that the difference in location between the on- and off-responses reflected differences in the relative strength of each activity between the two responses. In particular, it is important to note that the cPara activity of the on-response would have both the stimulus-driven component (stimulus-related) and the change detection (event-related) components.

As a candidate for a more posterior cortical source than the classical SII area of the off-response, the posterior insula (Davis et al., 1998), posterior parietal cortex (PPC) (Davis et al., 1998; Forss et al., 1994; Hari et al., 1990; Inui et al., 2004; Wegner et al., 2000) and TPJ are known to be activated by tactile stimuli. Among them, TPJ seems important since this area is sensitive to sensory changes (Downar et al., 2000, 2002). Although the present results did not find a significant difference in the location of the

source of activity between the on- and off-responses for iPara, the off-response tended to be located more posterior than the on-response similarly to the cPara source. This may be because the stimulus-driven component of iPara is relatively weak for both the on- and off-responses. Since the present study used stimulation of one side only, a definite conclusion based on the difference between iPara and cPara could not be drawn. The difference might come from contralateral/ipsilateral hemispheres or the left/right hemispheres.

Origin of the iPara activity

Our results showed that the peak latency of iPara was longer than that of cPara both for the on-response (7.6 ms, $p = 0.025$) and for the off-response (10.3 ms, $p = 0.098$), which suggested the difference in latency between cPara and iPara to come from the conduction of signals from the contralateral to ipsilateral hemisphere through the corpus callosum (Forss et al., 1999; Karhu and Tesche, 1999). However, since the off-response was not driven by sensory inputs, we should consider an activation mechanism for the iPara activity other than the standard

feedforward pathway with serial activation through SI, cPara and iPara. In addition, in some subjects of the present study, the cPara activity was ambiguous while the iPara activity was clear for the off-response. To explain these phenomena, we considered a processing stream of the change detecting system which is active after some fundamental sensory processing. In an fMRI study of hemispherectomized patients, Olausson et al. (2001) showed that iPara could be activated by painful stimuli without transcallosal transfer. Forss et al. (1999) also reported an MEG study in patients with stroke in which iPara could be activated without an activation in cPara. These previous findings together with the present results might suggest that the iPara activity is independent of the cPara activity for both the on- and off-responses.

Experiment 3: Auditory evoked magnetic fields (AEFs) study

In previous studies on auditory off-responses using EEG and MEG, it has been shown that the offset of a tone stimulus evokes a clear component similar to N1 (Hillyard and Picton, 1978) and N1m (Hari et al., 1987; Noda et al., 1998; Pantev et al., 1996; Wakai et al., 2007) of the on-response. The on-N1m and off-N1m components did not differ significantly in latency (Hari et al., 1987; Noda et al., 1998; Pantev et al., 1996) and the estimated dipoles were located close to each other (Hari et al., 1987; Noda et al., 1998; Pantev et al., 1996). Although off-N1m is considered to represent a response to abrupt auditory changes (Hari et al., 1987), the relationship between the on-response and off-response or physiological significance of the N1 component has been unclear.

Our recent EEG study on the somatosensory system (Yamashiro et al., 2008) showed that both the onset and offset of a train of electrical pulses elicited two components, P100 and N140, with a similar timing and topography. The latency of these two components of the off-response was determined precisely using the ODP. Therefore, we considered that both the on- and off-responses are triggered by abrupt change using a memory trace

with which the abrupt event (on or off) is compared with the preceding condition (silent or repetitive steady stimulus). In addition, an MEG study (Yamashiro et al., 2009) demonstrated a common cortical activation peaking at around 100 ms in the parasyylvian region between the on- and off-responses. This region of the somatosensory system is known to be responsible for higher order functions, such as attention, tactile texture discrimination, sensorimotor integration, and the integration of nociceptive and nonnociceptive inputs (for review, see Hari and Forss, 1999). Therefore, a cortical network for detecting changes is expected to exist in a higher sensory area in each modality. In fact, Downar et al., (2000) showed that unimodal and multimodal cortical areas relate to the detection of changes in the human somatosensory, auditory and visual systems using fMRI. In this fMRI study, the unimodal area related to this function was in higher order cortical areas than the primary sensory cortex.

Given that a cortical network relating to the detection of change is present in all sensory modalities, a similar component would be elicited by the onset and offset of a sensory stimulus of each modality. Although results of previous auditory studies (Hari et al., 1987; Noda et al., 1998;

Pantev et al., 1996;) appear to support the notion that a similar N1 component is elicited by the onset and offset of an auditory stimulus, whether this indicates the automatic detection of auditory changes still remains to be elucidated. In our recent study on the somatosensory system (Yamashiro et al., 2008), we used a train of electrical pulses (ISI: 10, 20, 50 ms) to investigate whether the on- and off-responses represent a similar event-type component relating to a somatosensory change. Results showed that a very similar component at around 100 ms was elicited by both the onset and offset of the stimulus train but the latency of the off-response was precisely dependent on the ISI, suggesting that this common component is triggered by a change event (on or off) and that short-term memory is involved in creating this automatic response, comparing a previous steady state and a new event. Therefore in this study, a similar stimulus train (ISI: LONG, 50, 100 ms) was used to investigate whether auditory on- and off-responses are an event-type response triggered automatically by an auditory change. The main objective of the present study was to examine whether a system for automatic detecting change is present in the auditory modality.

The auditory off-N1/N1m was slightly shorter than the on-N1/N1m in latency (Hari et al., 1987; Hillyard and Picton, 1978; Noda et al., 1998; Pantev et al., 1996), while the somatosensory off-P100 was slightly longer than the on-P100 by 14-24 ms (Yamashiro et al., 2008). Such a discrepancy may reflect the difference between the somatosensory and auditory modalities. We expected that we could know similarities and dissimilarities between the two modalities more precisely if we employ a similar stimulation paradigm.

In the auditory modality, there are two assumed lengths of the temporal window of integration (TWI) (Boemio et al., 2005). One is approximately 40-60 ms (Gage et al., 2006) and the other is 160-200 ms (Yabe et al., 1997, 1998, 2005). In this study, we expected that an off-N1m to the stimulus train could be elicited because the auditory system takes the stimulus train as a continuous stimulus (a unitary event) not separated events due to TWI.

Methods

Subjects

The experiments were performed on eleven (three female and eight male) healthy right-handed volunteers (25-45 years). The study was

approved in advance by the Ethics Committee of the National Institute for Physiological Sciences, Okazaki, Japan, and written consent was obtained from all the subjects.

Auditory stimulation

AEFs were elicited with a 1000 Hz pure tone of long duration (LONG) and a train of brief pure tones of the same frequency (duration 25 ms including 5 ms rise and fall times) applied to both the subject's ears. The frequency of the repetition of the brief tone was either 20 Hz or 10 Hz (Fig. 7A); that is, the ISI between each brief tone was 50 ms (ISI-50 ms) or 100 ms (ISI-100 ms). The ITI and stimulus duration were randomized between 3 and 5 s (Fig. 7B). The intensity of the stimulus was 60 dB above the threshold.

MEG recording and analysis

The experiments were carried out in a magnetically-shielded room. Subjects were instructed to watch a silent movie throughout the experiment. AEFs were recorded with a helmet-shaped 306-channel MEG system, which comprised 102 identical triple sensor elements. Each sensor element

consisted of two orthogonal planar gradiometers and one magnetometer coupled to a multi-SQUID and thus provided 3 independent measurements of the magnetic fields. In this study, we analyzed MEG signals recorded from 204 planar-type gradiometers. These planar gradiometers are powerful enough to detect the largest signal just over local cerebral sources. The signals were recorded with a bandpass of 0.1-200 Hz and digitized at 1000 Hz. The period of analysis for both the on- and off-responses was 500 ms including a prestimulus period of 100 ms that was used as the baseline. The off-response was triggered by the offset point of each tone. Trials with noise (> 2700 fT / cm) were rejected from the analysis automatically. For each on- and off-response, 100 artifact-free trials were recorded in each condition. The average data was filtered with a 1-50 Hz bandpass filter and then used for the analysis (Yabe et al., 2004, 2005).

To identify sources of the evoked activities, the ECD, which best explains the measured data, was computed by using a least-squares search. A subset of 14-20 channels including the local signal maxima was used for the estimation of ECDs (Forss et al. 1998, Nakata et al. 2005, Wasaka et al. 2005). These calculations gave the three-dimensional (3D) location, orientation, and strength of the ECD in a spherical conductor model, which was based on each subject's MRI scan to show the source's location. The

goodness-of-fit value of an ECD was calculated to indicate in percentage terms how much the dipole accounts for the measured field variance. Model adequacy was assessed by examining variance (Hari et al., 1988). Only ECDs explaining more than 80% of the field variance at selected points in time were used for further analysis. The period of analysis was extended to the entire time period and all channels were taken into account when computing a time-varying multi-dipole model. The strength of the previously found ECDs was allowed to change while their locations and orientations were kept fixed. The data acquisition and analysis followed Hämäläinen et al., (1993). MRI scans were obtained from all subjects with a 3.0-T Siemens Allegra scanner. T1-weighted coronal, axial and sagittal image slices obtained every 1.5 mm were used for rendering the 3D reconstruction of the brain's surface. Prior to the recording, a current was fed to four HPI coils placed at known sites to obtain the exact location of the head with respect to the sensor and the resulting magnetic fields were measured with the magnetometer, which allowed for aligning the individual head coordinate systems with the magnetometer coordinate system. The four HPI coils attached to the subject's head were measured with respect to three anatomical landmarks using a 3D digitizer to allow alignment of the MEG and MRI. The x-axis was fixed with the preauricular points, the

positive direction being to the right. The positive y-axis passed through the nasion and the z-axis thus pointed upward.

The peak latency of each cortical activity was subjected to a three-way repeated measure ANOVA (hemisphere x event x ISI). The Greenhouse-Geisser epsilon was used to correct the degrees of freedom. The statistical significance of the source's location was assessed by a discriminant analysis using x, y, and z coordinates as variables for each condition. The source's orientation was also assessed by a discriminant analysis using x, y, and z vectors as variables for each condition. The relationship in amplitude between the on- and off-responses across all the subjects was assessed under the three conditions by determining a correlation coefficient, r .

Results

Waveform and source

Figure 8 shows the on- and off-responses in a representative subject. In ten of eleven subjects, a clear and consistent component was evoked in two cortical areas (Fig. 8) by the onset and offset of the stimulation. Although a train of brief tones was presented in ISI-50 ms and ISI-100 ms, the onset of

the stimulus evoked a very similar N1m component in all three conditions. The field distribution was also similar between the on- and off-responses. By an ECD analysis, dipoles responsible for these responses were estimated to be located around the STG of both hemispheres. The location and orientation of the source were not significantly different between the on- and off-responses for all conditions (Table 4, Fig. 9B).

Time course of the cortical activity

Figure 9A shows the strength of the source of activity for the on- and off-responses of ten subjects as a function of time. Table 5 shows the mean peak latency and amplitude of the cortical activity. A three-way ANOVA (hemisphere x event x ISIs) indicated event (on or off) and ISI (LONG, ISI-50 ms and ISI-100 ms) to be significant factors determining the peak latency of the activity ($F_{(1,9)} = 47$ $p < 0.001$ $\epsilon = 1$, $F_{(2, 18)} = 500$ $p < 0.001$ $\epsilon = 0.5$). As shown in Fig. 9A and Table 5, the peak latency of the activity in the STG did not differ among the three ISIs for the on-response, while it clearly increased with an increase in ISI for the off-response. The mean peak latency of the activity in the Lt-STG for the off-response was 84, 124

and 183 ms for LONG, ISI-50 ms and ISI-100 ms, respectively. The respective peak latency of the activity in the Rt-STG was 83, 123 and 182 ms. That is, the off-response was precisely determined by the ODP where the brain knows theoretically that the stimulus ends.

Relationship between the on- and off-responses among the subjects

When the relationship of the amplitude of the STG-derived activity between the on- and off-responses was compared across subjects for each condition, the correlation coefficient, r , was 0.80 ($p = 0.0002$), 0.58 ($p = 0.007$) and 0.61 ($p = 0.005$) for LONG, ISI-50 ms and ISI-100 ms, respectively (Fig. 10). The slope of the regression line (off/on) was 0.44, 0.43 and 0.46, respectively.

Discussion

In the present study, we examined using AEFs in humans whether the abrupt onset and offset of sensory stimulation activated a similar cortical network to test our hypothesis that any changes in the sensory environment should be detected automatically to draw attention and facilitate the execution of appropriate behavior (Yamashiro et al., 2008, 2009). The

present results were consistent with the hypothesis showing, that i) a very similar N1m component was elicited by the onset of tone irrespective of the type of stimulus (long duration or repetitive), ii) the offset of stimuli elicited a component very similar to on-N1m, iii) the latency of off-N1m was precisely determined by the ISI, indicating that this component was based on short-term memory of the stimulus frequency, and iv) there was a significant positive correlation between the amplitude of on-N1m and amplitude of off-N1m, suggesting that the on-N1m and off-N1m components originate from a similar group of neurons or even identical neurons.

ON-N1m component

As shown in Figs. 8 and 9, a very similar on-N1m component was elicited by the LONG, ISI-50 ms and ISI-100 ms tones, indicating that N1m is a response to the abrupt onset of the stimulus. We refer to this type of response as an ‘event-related response’ in this paper. It is well recognized that a N1 component similar to that in the present study is also evoked by a brief sound such as a click (Joutsiniemi et al. 1989; Picton et al., 1974). In

addition to the N1 component, a sharp activity originating from the primary auditory cortex (PAC) that responds to each brief tone faithfully is considered to have helped shape the on-response following the ISI-50 ms and ISI-100 ms tones (stimulus-related response). Previous MEG and intracranial recording studies showed an activity in the PAC responding faithfully to high frequency tones (Brugge et al., 2008; Gutschalk et al., 1999). In the somatosensory system, such responses were evoked by a train of electrical pulses in the primary somatosensory cortex (Forss et al., 2001; Hamada et al., 2002; Hoshiyama and Kakigi, 2003; Nangini et al., 2006; Wikstrom et al., 1996). Therefore, these responses seemed to be locked by each pulse to produce temporally and spatially accurate information about the stimuli. The reason why a stimulus-locked activity in the PAC was not observed in the present study was likely due to its location deep in the PAC and small amplitude (Godey et al., 2001; Liegeois-Chauvel et al., 1991; Yvert et al., 2001).

N1m (Hari et al., 1982) or activity in the STG (Howard et al., 2000; Tanaka et al., 2008) is sensitive to stimulus rate. That is, its amplitude increases with a decrease in the stimulus rate. Given that the on-N1m

component is a response to auditory changes, this finding is quite natural since a longer stimulus interval indicates an abrupt break of a longer silent period. The idea that N1m is an automatic response to an auditory change can also explain why only a single N1m component of a similar duration is evoked by any type of auditory stimulus (brief, long, continuous, repetitive and so on). In fact, the STG was shown to be sensitive to a change in sound in an fMRI study (Downar et al., 2000).

OFF-N1m component

The peak latency of on-N1m and off-N1m under LONG was consistent with previous studies (Hari et al., 1987; Noda et al., 1998; Pantev et al., 1996) showing that the peak latency of off-N1 was slightly shorter than that of on-N1m. The off-N1m component was triggered by the cessation of the tone irrespective of the stimulus type, suggesting that off-N1m is also an event-related response. In addition, the latency of off-N1m was determined not by the timing of the last pulse but precisely by the latency point of the last pulse plus ISI and off-N1m was elicited without the subject's attention, indicating that the off-N1m component is an automatic memory-based

event-related response (Figs. 8 and 9A). This notion is supported by the fact that the amplitude of off-N1 increased with an increase in the duration of the tone's presentation (Hillyard and Picton, 1978). The present results on the latency of off-N1m completely replicated a previous EEG study (Jones, 1992) using a click stimulus. Jones (1992) proposed that potentials are due to a higher order of neurons that automatically respond to the occurrence of a “mismatch” between an immediate sound and a sound image that was previously present, encoded in short-term memory.

In the auditory domain, there are two assumed lengths of the TWI (Boemio et al., 2005). Previous MEG studies showed that one is approximately 40-60 ms (Gage et al., 2006) and the other is 160-200 ms (Yabe et al., 1997, 1998, 2005). The shorter TWI modulates the latency and amplitude of the on-N1m (Gage et al., 2006), while the longer TWI appears to be related the omission response (Yabe et al., 1997, 1998). The off-N1m of present study was dependent on the ISI (50 ms and 100 ms) of the stimulus train and therefore seems to be related to the longer TWI. Yabe et al. (1998) investigated an auditory omission response using six different stimulus-onset asynchronies (SOAs; 100, 125, 150, 175, 200 and 350 ms)

and demonstrated that a definite magnetic mismatch negativity (MMNm) was elicited by the stimulus omission only with the three shortest SOAs (100, 125 and 150 ms). They suggested that 160-170 ms was the TWI used by the auditory system in integrating successive auditory inputs into auditory percepts. This finding might support that a longer TWI was needed to detect abrupt absence of an expected stimulus using short term memory (that is, the missing stimulus at ODP). The off-response triggered by the offset of the 10Hz-tone in the present study (ODP of 100 ms) appears to correspond to the omission response at an SOA of 100 ms in Yabe's study (Yabe et al., 1998). Therefore, the present results do not exclude the possibility that the off-N1m to the stimulus train is at least a part of MMNm (see Näätänen and Picton., 1987)

Comparison of on-N1m and off-N1m

In the present study, on-N1m and off-N1m did not differ in the location or orientation of their sources, suggesting that they originate from a similar group of neurons or even identical neurons. This result was consistent with previous auditory studies (Hari et al., 1987; Noda et al., 1998; Pantev et al.,

1996). Since the time course of activation, location and orientation were very similar between on-N1m and off-N1m, these components seem to be a response to abrupt auditory changes elicited by comparing the abrupt event (on or off) with the preceding condition (silent or preceding sound), and therefore, have similar physiological significance and mechanisms. The significant correlation of amplitude between on-N1m and off-N1m in the present study supported this notion.

In previous studies using MEG to investigate auditory (Inui and Kakigi, 2006), tactile (Inui et al., 2004), pain (Inui et al., 2003a,b) and visual (Inui et al., 2006a,b) systems, we found a similar sequential activation pattern through “early” and “late” sensory cortical areas among these sensory modalities. In general, the “late” activity i) appears after several “early” activities, ii) has a longer duration than the “early” activities, iii) shows sensitivity to the ISI, iv) is followed by sensory-nonspecific vertex potentials and v) has an activation profile that is difficult to explain with a standard feedforward pathway (Inui and Kakigi, 2006; Tanaka et al., 2008). Such “late” cortical areas include the STG (auditory), parasyylvian region (tactile and pain) and middle occipital gyrus (visual). Since we have

already found that the parasyllvian region (tactile, Yamashiro et al., 2009) and STG (this study) are involved in the detection of changes, this function may be one more important common feature of the “late” activity. Further study of the nociceptive and visual systems may confirm this notion.

General conclusion

In the present three studies, we could investigate the on- and off-responses by use of EEG and MEG in the somatosensory and auditory modalities. The results showed that i) a very similar components were elicited by the onset and offset of stimulation in the somatosensory and auditory modalities, ii) the latency of off-responses was precisely determined by the ISI in the somatosensory and auditory modalities, iii) dipoles responsible for on- and off-responses were estimated to be located around higher sensory cortical area in each modality, iv) there was a significant positive correlation between the amplitude of on- and off-responses in the auditory modality. Based on the present results, we concluded that at least some of the on- and off-responses in the somatosensory and auditory systems arise from a common cortical network sensitive to sensory changes. In this network, the change is automatically detected by comparing the abrupt event with the preceding condition and the main generator is located around higher sensory area in each sensory modality.

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Reference

Ahissar, E., Sosnik, R., Haidarliu, S., 2000. Transformation from temporal to rate coding in a somatosensory thalamocortical pathway. *Nature* 406, 302-306.

Akatsuka, K., Wasaka, T., Nakata, H., Inui, K., Hoshiyama, M., Kakigi, R., 2005. Mismatch responses related to temporal discrimination of somatosensory stimulation. *Clin Neurophysiol* 116, 1930-1937.

Akatsuka, K., Wasaka, T., Nakata, H., Kida, T., Hoshiyama, M., Tamura, Y., Kakigi, R., 2007. Objective examination for two-point stimulation using a somatosensory oddball paradigm: an MEG study. *Clin Neurophysiol* 118, 403-411.

Allison, T., McCarthy, G., Wood, C.C., 1992. The relationship between human long-latency somatosensory evoked potentials recorded from the cortical surface and from the scalp. *Electroencephalogr Clin Neurophysiol* 84, 301-314.

Allison, T., McCarthy, G., Wood, C.C., Williamson, P.D., Spencer, D.D., 1989. Human cortical potentials evoked by stimulation of the median nerve. II. Cytoarchitectonic areas generating long-latency activity. *J Neurophysiol* 62, 711-722.

Boemio, A., Fromm, S., Braun, A., Poeppel, D., 2005. Hierarchical and asymmetric temporal sensitivity in human auditory cortices. *Nat Neurosci* 8, 389-395.

Brugge, J.F., Volkov, I.O., Oya, H., Kawasaki, H., Reale, R.A., Fenoy, A., Steinschneider, M., Howard, M.A., 3rd, 2008. Functional localization of auditory cortical fields of human: click-train stimulation. *Hear Res* 238, 12-24.

Burton, H., MacLeod, A.M., Videen, T.O., Raichle, M.E., 1997. Multiple foci in parietal and frontal cortex activated by rubbing embossed grating patterns across fingerpads: a positron emission tomography study in humans. *Cereb Cortex* 7, 3-17.

Burton, H., Videen, T.O., Raichle, M.E., 1993. 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.

Crevits, L., van Lith, G., Viifvinkel-Bruinenga, S., 1982. On and off contribution to the combined occipital on-off response to a pattern stimulus. *Ophthalmologica* 184, 169-173.

Davis, K.D., Kwan, C.L., Crawley, A.P., Mikulis, D.J., 1998. Functional

MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. *J Neurophysiol* 80, 1533-1546.

Derdikman, D., Yu, C., Haidarliu, S., Bagdasarian, K., Arieli, A., Ahissar, E., 2006. Layer-specific touch-dependent facilitation and depression in the somatosensory cortex during active whisking. *J Neurosci* 26, 9538-9547.

Desmedt, J.E., Robertson, D., 1977. Differential enhancement of early and late components of the cerebral somatosensory evoked potentials during forced-paced cognitive tasks in man. *J Physiol* 271, 761-782.

Desmedt, J.E., Tomberg, C., 1989. Mapping early somatosensory evoked potentials in selective attention: critical evaluation of control conditions used for titrating by difference the cognitive P30, P40, P100 and N140. *Electroencephalogr Clin Neurophysiol* 74, 321-346.

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.

Disbrow, E., Roberts, T., Poeppel, D., Krubitzer, L., 2001. Evidence for interhemispheric processing of inputs from the hands in human S2 and PV. *J Neurophysiol* 85, 2236-2244.

Downar, J., Crawley, A.P., Mikulis, D.J., Davis, K.D., 2000. A multimodal cortical network for the detection of changes in the sensory environment. *Nat Neurosci* 3, 277-283.

Downar, J., Crawley, A.P., Mikulis, D.J., Davis, K.D., 2002. A cortical network sensitive to stimulus salience in a neutral behavioral context across multiple sensory modalities. *J Neurophysiol* 87, 615-620.

Downar, J., Mikulis, D.J., Davis, K.D., 2003. Neural correlates of the prolonged salience of painful stimulation. *Neuroimage* 20, 1540-1551.

Eickhoff, S.B., Grefkes, C., Zilles, K., Fink, G.R., 2007. The somatotopic organization of cytoarchitectonic areas on the human parietal operculum. *Cereb Cortex* 17, 1800-1811.

Ferretti, A., Babiloni, C., Arienzo, D., Del Gratta, C., Rossini, P.M., Tartaro, A., Romani, G.L., 2007. Cortical brain responses during passive nonpainful median nerve stimulation at low frequencies (0.5-4 Hz): an fMRI study. *Hum Brain Mapp* 28, 645-653.

Forss, N., Hari, R., Salmelin, R., Ahonen, A., Hamalainen, M., Kajola, M., Knuutila, J., Simola, J., 1994. Activation of the human posterior parietal cortex by median nerve stimulation. *Exp Brain Res* 99, 309-315.

Forss, N., Hietanen, M., Salonen, O., Hari, R., 1999. Modified activation of somatosensory cortical network in patients with right-hemisphere stroke. *Brain* 122 (Pt 10), 1889-1899.

Forss, N., Jousmaki, V., 1998. Sensorimotor integration in human primary and secondary somatosensory cortices. *Brain Res* 781, 259-267.

Forss, N., Narici, L., Hari, R., 2001. Sustained activation of the human SII cortices by stimulus trains. *Neuroimage* 13, 497-501.

Frot, M., Garcia-Larrea, L., Guenet, M., Mauguiere, F., 2001. Responses of the supra-sylvian (SII) cortex in humans to painful and innocuous stimuli. A study using intra-cerebral recordings. *Pain* 94, 65-73.

Frot, M., Mauguiere, F., 1999. Timing and spatial distribution of somatosensory responses recorded in the upper bank of the sylvian fissure (SII area) in humans. *Cereb Cortex* 9, 854-863.

Gage, N., Roberts, T.P., Hickok, G., 2006. Temporal resolution properties of human auditory cortex: reflections in the neuromagnetic auditory evoked M100 component. *Brain Res* 1069, 166-171.

Godey, B., Schwartz, D., de Graaf, J.B., Chauvel, P., Liegeois-Chauvel, C., 2001. Neuromagnetic source localization of auditory evoked fields and

intracerebral evoked potentials: a comparison of data in the same patients. *Clin Neurophysiol* 112, 1850-1859.

Gutschalk, A., Mase, R., Roth, R., Ille, N., Rupp, A., Hahnel, S., Picton, T.W., Scherg, M., 1999. Deconvolution of 40 Hz steady-state fields reveals two overlapping source activities of the human auditory cortex. *Clin Neurophysiol* 110, 856-868.

Hamada, Y., Otsuka, S., Okamoto, T., Suzuki, R., 2002. The profile of the recovery cycle in human primary and secondary somatosensory cortex: a magnetoencephalography study. *Clin Neurophysiol* 113, 1787-1793.

Hämäläinen, M., Hari, R., Ilmoniemi, R.J., Knuutila, J., Lounasmaa, O.V., 1993. Magnetoencephalography—theory, instrumentation, and applications to noninvasive studies of the working human brain. *Reviews of Modern Physics* 65, 413.

Hari, R., Forss, N., 1999. Magnetoencephalography in the study of human somatosensory cortical processing. *Philos Trans R Soc Lond B Biol Sci* 354, 1145-1154.

Hari, R., Hämäläinen, H., Hämäläinen, M., Kekoni, J., Sams, M., Tiihonen, J., 1990. Separate finger representations at the human second somatosensory cortex. *Neuroscience* 37, 245-249.

Hari, R., Joutsiniemi, S.L., Sarvas, J., 1988. Spatial resolution of neuromagnetic records: theoretical calculations in a spherical model. *Electroencephalogr Clin Neurophysiol* 71, 64-72.

Hari, R., Kaila, K., Katila, T., Tuomisto, T., Varpula, T., 1982. Interstimulus interval dependence of the auditory vertex response and its magnetic counterpart: implications for their neural generation. *Electroencephalogr Clin Neurophysiol* 54, 561-569.

Hari, R., Pelizzone, M., Makela, J.P., Hallstrom, J., Leinonen, L., Lounasmaa, O.V., 1987. Neuromagnetic responses of the human auditory cortex to on- and offsets of noise bursts. *Audiology* 26, 31-43.

Hillyard, S.A., Picton, T.W., 1978. On and off components in the auditory evoked potential. *Percept Psychophys* 24, 391-398.

Hoshiyama, M., Kakigi, R., 2003. Changes in somatosensory evoked responses by repetition of the median nerve stimulation. *Clin Neurophysiol* 114, 2251-2257.

Howard, M.A., Volkov, I.O., Mirsky, R., Garell, P.C., Noh, M.D., Granner, M., Damasio, H., Steinschneider, M., Reale, R.A., Hind, J.E., Brugge, J.F., 2000. Auditory cortex on the human posterior superior temporal gyrus. *J Comp Neurol* 416, 79-92.

Inoue, K., Yamashita, T., Harada, T., Nakamura, S., 2002. Role of human SII cortices in sensorimotor integration. *Clin Neurophysiol* 113, 1573-1578.

Inui, K., Kakigi, R., 2006. Temporal analysis of the flow from V1 to the extrastriate cortex in humans. *J Neurophysiol* 96, 775-784.

Inui, K., Okamoto, H., Miki, K., Gunji, A., Kakigi, R., 2006a. Serial and parallel processing in the human auditory cortex: a magnetoencephalographic study. *Cereb Cortex* 16, 18-30.

Inui, K., Sannan, H., Miki, K., Kaneoke, Y., Kakigi, R., 2006b. Timing of early activity in the visual cortex as revealed by simultaneous MEG and ERG recordings. *Neuroimage* 30, 239-244.

Inui, K., Tran, T.D., Qiu, Y., Wang, X., Hoshiyama, M., Kakigi, R., 2003a. A comparative magnetoencephalographic study of cortical activations evoked by noxious and innocuous somatosensory stimulations. *Neuroscience* 120, 235-248.

Inui, K., Wang, X., Qiu, Y., Nguyen, B.T., Ojima, S., Tamura, Y., Nakata, H., Wasaka, T., Tran, T.D., Kakigi, R., 2003b. Pain processing within the primary somatosensory cortex in humans. *Eur J Neurosci* 18, 2859-2866.

Inui, K., Wang, X., Tamura, Y., Kaneoke, Y., Kakigi, R., 2004. Serial processing in the human somatosensory system. *Cereb Cortex* 14, 851-857.

Jones, S.J., 1992. AEPs at the onset and offset of repetitive sound modulation, due to mismatch with the contents of an auditory sensory store. *Electroencephalogr Clin Neurophysiol* 84, 149-156.

Joutsiniemi, S.L., Hari, R., Vilkmann, V., 1989. Cerebral magnetic responses to noise bursts and pauses of different durations. *Audiology* 28, 325-333.

Karhu, J., Tesche, C.D., 1999. Simultaneous early processing of sensory input in human primary (SI) and secondary (SII) somatosensory cortices. *J Neurophysiol* 81, 2017-2025.

Kekoni, J., Hämäläinen, H., McCloud, V., Reinikainen, K., Näätänen, R., 1996. Is the somatosensory N250 related to deviance discrimination or conscious target detection? *Electroencephalogr Clin Neurophysiol* 100, 115-125.

Kekoni, J., Hämäläinen, H., Saarinen, M., Grohn, J., Reinikainen, K., Lehtokoski, A., Näätänen, R., 1997. Rate effect and mismatch responses in the somatosensory system: ERP-recordings in humans. *Biol Psychol* 46, 125-142.

Kida, T., Nishihira, Y., Wasaka, T., Nakata, H., Sakamoto, M., 2004. Passive enhancement of the somatosensory P100 and N140 in an active attention task using deviant alone condition. *Clin Neurophysiol* 115, 871-879.

Kida, T., Wasaka, T., Inui, K., Akatsuka, K., Nakata, H., Kakigi, R., 2006a. Centrifugal regulation of human cortical responses to a task-relevant somatosensory signal triggering voluntary movement. *Neuroimage* 32, 1355-1364.

Kida, T., Wasaka, T., Nakata, H., Akatsuka, K., Kakigi, R., 2006b. Active attention modulates passive attention-related neural responses to sudden somatosensory input against a silent background. *Exp Brain Res* 175, 609-617.

Ledberg, A., O'Sullivan, B.T., Kinomura, S., Roland, P.E., 1995. Somatosensory activations of the parietal operculum of man. A PET study. *Eur J Neurosci* 7, 1934-1941.

Liegeois-Chauvel, C., Musolino, A., Chauvel, P., 1991. Localization of the primary auditory area in man. *Brain* 114 (Pt 1A), 139-151.

Lin, Y.Y., Forss, N., 2002. Functional characterization of human second somatosensory cortex by magnetoencephalography. *Behav Brain Res* 135, 141-145.

Mauguiere, F., Merlet, I., Forss, N., Vanni, S., Jousmaki, V., Adeleine, P., Hari, R., 1997a. Activation of a distributed somatosensory cortical network in the human brain. A dipole modelling study of magnetic fields evoked by median nerve stimulation. Part I: Location and activation timing of SEF sources. *Electroencephalogr Clin Neurophysiol* 104, 281-289.

Mauguiere, F., Merlet, I., Forss, N., Vanni, S., Jousmaki, V., Adeleine, P., Hari, R., 1997b. Activation of a distributed somatosensory cortical network in the human brain: a dipole modelling study of magnetic fields evoked by median nerve stimulation. Part II: Effects of stimulus rate, attention and stimulus detection. *Electroencephalogr Clin Neurophysiol* 104, 290-295.

McCarthy, G., Luby, M., Gore, J., Goldman-Rakic, P., 1997. Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. *J Neurophysiol* 77, 1630-1634.

McGlone, F., Kelly, E.F., Trulsson, M., Francis, S.T., Westling, G., Bowtell, R., 2002. Functional neuroimaging studies of human somatosensory cortex. *Behav Brain Res* 135, 147-158.

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., 1957. Modality and topographic properties of single neurons of cat's somatic sensory cortex. *J Neurophysiol* 20, 408-434.

Näätänen, R., Jacobsen, T., Winkler, I., 2005. Memory-based or afferent processes in mismatch negativity (MMN): a review of the evidence. *Psychophysiology* 42, 25-32.

Näätänen, R., Paavilainen, P., Reinikainen, K., 1989. Do event-related potentials to infrequent decrements in duration of auditory stimuli demonstrate a memory trace in man? *Neurosci Lett* 107, 347-352.

Näätänen, R., Picton, T., 1987. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. *Psychophysiology* 24, 375-425.

Nakata, H., Inui, K., Wasaka, T., Akatsuka, K., Kakigi, R., 2005. Somato-motor inhibitory processing in humans: a study with MEG and ERP. *Eur J Neurosci* 22, 1784-1792.

Nangini, C., Ross, B., Tam, F., Graham, S.J., 2006. Magnetoencephalographic study of vibrotactile evoked transient and steady-state responses in human somatosensory cortex. *Neuroimage* 33, 252-262.

Noda, K., Tonoike, M., Doi, K., Koizuka, I., Yamaguchi, M., Seo, R., Matsumoto, N., Noiri, T., Takeda, N., Kubo, T., 1998. Auditory evoked off-response: its source distribution is different from that of on-response. *Neuroreport* 9, 2621-2625.

Olausson, H., Ha, B., Duncan, G.H., Morin, C., Ptito, A., Ptito, M., Marchand, S., Bushnell, M.C., 2001. Cortical activation by tactile and painful stimuli in hemispherectomized patients. *Brain* 124, 916-927.

Pantev, C., Eulitz, C., Hampson, S., Ross, B., Roberts, L.E., 1996. The auditory evoked "off" response: sources and comparison with the "on" and the "sustained" responses. *Ear Hear* 17, 255-265.

Picton, T.W., Hillyard, S.A., Krausz, H.I., Galambos, R., 1974. Human auditory evoked potentials. I. Evaluation of components. *Electroencephalogr Clin Neurophysiol* 36, 179-190.

Ploner, M., Schmitz, F., Freund, H.J., Schnitzler, A., 1999. Parallel activation of primary and secondary somatosensory cortices in human pain processing. *J Neurophysiol* 81, 3100-3104.

Shinozaki, N., Yabe, H., Sutoh, T., Hiruma, T., Kaneko, S., 1998. Somatosensory automatic responses to deviant stimuli. *Brain Res Cogn Brain Res* 7, 165-171.

Sinclair, R.J., Burton, H., 1991. Neuronal activity in the primary somatosensory cortex in monkeys (*Macaca mulatta*) during active touch of textured surface gratings: responses to groove width, applied force, and velocity of motion. *J Neurophysiol* 66, 153-169.

Spackman, L., Boyd, S., Towell, T., 2006. Identification and characterization of somatosensory off responses. *Brain Res* 1114, 53-62.

Sur, M., Wall, J.T., Kaas, J.H., 1984. Modular distribution of neurons with slowly adapting and rapidly adapting responses in area 3b of somatosensory cortex in monkeys. *J Neurophysiol* 51, 724-744.

Tanaka, E., Inui, K., Kida, T., Miyazaki, T., Takeshima, Y., Kakigi, R., 2008. A transition from unimodal to multimodal activations in four sensory modalities in humans: an electrophysiological study. *BMC Neurosci* 9, 116.

Torquati, K., Pizzella, V., Babiloni, C., Del Gratta, C., Della Penna, S., Ferretti, A., Franciotti, R., Rossini, P.M., Romani, G.L., 2005. Nociceptive and non-nociceptive sub-regions in the human secondary somatosensory cortex: an MEG study using fMRI constraints. *Neuroimage* 26, 48-56.

Wakai, R.T., Lutter, W.J., Chen, M., Maier, M.M., 2007. On and Off magnetic auditory evoked responses in early infancy: a possible marker of

brain immaturity. *Clin Neurophysiol* 118, 1480-1487.

Wasaka, T., Kida, T., Nakata, H., Akatsuka, K., Kakigi, R., 2007. Characteristics of sensori-motor interaction in the primary and secondary somatosensory cortices in humans: a magnetoencephalography study. *Neuroscience* 149, 446-456.

Wasaka, T., Nakata, H., Akatsuka, K., Kida, T., Inui, K., Kakigi, R., 2005. Differential modulation in human primary and secondary somatosensory cortices during the preparatory period of self-initiated finger movement. *Eur J Neurosci* 22, 1239-1247.

Wegner, K., Forss, N., Salenius, S., 2000. Characteristics of the human contra- versus ipsilateral SII cortex. *Clin Neurophysiol* 111, 894-900.

Wikstrom, H., Huttunen, J., Korvenoja, A., Virtanen, J., Salonen, O., Aronen, H., Ilmoniemi, R.J., 1996. Effects of interstimulus interval on somatosensory evoked magnetic fields (SEFs): a hypothesis concerning SEF generation at the primary sensorimotor cortex. *Electroencephalogr Clin Neurophysiol* 100, 479-487.

Yabe, H., Asai, R., Hiruma, T., Sutoh, T., Koyama, S., Kakigi, R., Tervaniemi, M., Kaneko, S., 2004. Sound perception affected by nonlinear variation of accuracy in memory trace. *Neuroreport* 15, 2813-2817.

Yabe, H., Matsuoka, T., Sato, Y., Hiruma, T., Sutoh, T., Koyama, S., Gunji, A., Kakigi, R., Kaneko, S., 2005. Time may be compressed in sound representation as replicated in sensory memory. *Neuroreport* 16, 95-98.

Yabe, H., Tervaniemi, M., Reinikainen, K., Naatanen, R., 1997. Temporal window of integration revealed by MMN to sound omission. *Neuroreport* 8, 1971-1974.

Yabe, H., Tervaniemi, M., Sinkkonen, J., Huotilainen, M., Ilmoniemi, R.J., Naatanen, R., 1998. Temporal window of integration of auditory information in the human brain. *Psychophysiology* 35, 615-619.

Yamashiro, K., Inui, K., Otsuru, N., Kida, T., Akatsuka, K., Kakigi, R., 2008. Somatosensory off-response in humans: an ERP study. *Exp Brain Res* 190, 207-213.

Yamashiro, K., Inui, K., Otsuru, N., Kida, T., Kakigi, R., 2009. Somatosensory off-response in humans: an MEG study. *Neuroimage* 44, 1363-1368.

Yvert, B., Crouzeix, A., Bertrand, O., Seither-Preisler, A., Pantev, C., 2001. Multiple supratemporal sources of magnetic and electric auditory evoked middle latency components in humans. *Cereb Cortex* 11, 411-423.

Tables

Table1. The mean peak latency of P100 and N140 in Experiment 1 and 2

Latency (ms)	20Hz		50Hz		100Hz	
	On	Off	On	Off	On	Off
Exp1						
P100						
Fz	88(11)	155(14)	85(14)	118(13)	89(12)	113(11)
Cz	86(12)	159(18)	86(14)	121(6)	85(15)	115(9)
Pz	97(14)	161(18)	97(12)	131(12)	89(12)	117(13)
N140						
Fz	151(22)	215(15)	146(14)	192(9)	148(11)	176(10)
Cz	149(18)	222(22)	145(14)	193(10)	141(14)	173(11)
Pz	156(18)	221(33)	150(18)	198(14)	146(16)	184(25)
Exp2						
P100						
Fz	86(17)	146(10)	91(12)	118(12)	94(13)	111(11)
Cz	87(9)	153(12)	89(13)	123(8)	86(12)	113(12)
Pz	96(16)	160(10)	96(12)	126(11)	92(13)	114(14)
N140						
Fz	154(18)	223(13)	153(10)	179(12)	151(9)	174(15)
Cz	156(14)	213(17)	149(11)	177(16)	150(15)	172(15)
Pz	163(12)	216(18)	150(11)	182(18)	158(10)	184(13)

Data are expressed as mean values (standard deviations)

Table 2. Locations of the dipoles for the on- and off-responses.

		x	y	z
On-response	SI	-45.7±5.0	17.0±10.4	95.8±5.3
	cPara	-53.5±6.9	27.9±7.6	68.6±5.9
	iPara	46.3±9.6	27.0±6.6	68.1±8.3
Off-response	cPara	-47.8±6.8	17.8±7.6	78.1±8.1
	iPara	48.6±8.9	21.9±12.9	73.1±8.6

Data are expressed as the mean \pm SD. The x-axis was fixed with the preauricular points, the positive direction being to the right. The positive y-axis passed through the nasion and the z-axis thus pointed upward

Table 3. The peak latency and amplitude of each cortical activity.

	Early SI	late SI	cPara	iPara
latency				
On	34±2.6	105.6±24.4	114.6±17.4	122.4±21.9
Off			133.9±14.2	144.1±17.8
amplitude				
On	8.4±6.3	29.4±19.3	39.0±28.3	22.7±14.4
Off			17.1±7.4	12.6±10.8

Data are expressed as the mean \pm SD. SI, primary somatosensory cortex; cPara, contralateral parasyylvian region; iPara, ipsilateral parasyylvian region.

Table 4. Locations of the dipoles for the on- and off-responses under the three conditions.

	ON			OFF		
	x	y	z	x	y	z
Lt-STG						
LONG	-54.1	10.2	57.2	-57	12.2	55.4
ISI50 ms	-54.3	9.6	56.3	-54.7	8.7	56.9
ISI100 ms	-54.6	10.1	55.6	-57.6	11.7	55
Rt-STG						
LONG	52.1	20.6	55.4	54	19.6	54.8
ISI50 ms	52.6	21.1	56.2	52.1	18.8	54.8
ISI100 ms	52.5	19	54.6	51.7	17.5	54.8

Data are expressed as the mean. The x-axis was fixed with the preauricular points, the positive direction being to the right. The positive y-axis passed through the nasion and the z-axis thus pointed upward. Rt-STG, right superior temporal gyrus; Lt-STG, left superior temporal gyrus;

Table 5. The peak latency and amplitude of each cortical source under the three conditions.

	ON		OFF	
	Lt-STG	Rt-STG	Lt-STG	Rt-STG
Latency (ms)				
LONG	105±9.9	102±6.6	84±8.6	83±7.8
ISI50 ms	107±11.2	112±10.9	124±8.1	123±6.7
ISI100 ms	110±11	111±7.6	183±10.9	182±9.8
Amplitude (nAm)				
LONG	51±21.5	55±20.7	17±11.3	22±12.6
ISI50 ms	41±13.8	50±18.4	20±9.4	27±13.9
ISI100 ms	44±14.3	49±17.1	14±9.0	21±13.8

Data are expressed as the mean ± SD. Rt-STG, right superior temporal gyrus; Lt-STG, left superior temporal gyrus;

Figures

Figure 1. On- and off-responses in a single trial in a representative subject.

Figure 2. Grand-averaged waveforms at Cz elicited by the onset and offset of stimulation at three different interstimulus intervals in Experiment 1 and Experiment 2. Arrowheads indicate the offset-discriminating point. ITI, inter-trial interval.

Figure 3. Grand-averaged waveforms across subjects of all the 15 electrodes in Experiment 2. The on-response (black line) is the average of all three ISI waveforms. The off-response (gray line) is the average of ODP-corrected waveforms of the three ISI waveforms.

Figure 4. Magnetic fields evoked by the onset (A) and offset (B) of somatosensory stimulation. Data from a representative subject: a top view of traces of all the sensors. In each response pair, the upper trace illustrates the field derivate along the latitude and the lower trace that along the longitude. C, enlarged waveforms of sensors indicated by circles in A and B.

In this figure and Fig.3, waveforms of the SI area show the stimulus-driven sharp activity at 50 Hz. Note the similar time course of the activity in the parasyylvian region between the on- and off-responses, and similar amplitude of the ipsilateral response (c) between the on- and off-responses.

Figure 5. Comparison of the location of the dipole in the parasyylvian (Para) region between the on- and off-responses. A and B, the mean location of cPara and iPara activities in response to the onset and offset of the stimulus in the x-y axis (A) and x-z axis (B). C and D, location of each dipole superimposed on the subject's own MR images in eight subjects. For comparison of the source's location, all dipoles are plotted on images for the on-response. Error bars show the SD.

Figure 6. Time course of the strength of each cortical activity elicited by the onset (A) and offset (B) of somatosensory stimulation. Data from a representative subject. Right columns (C and D) show the location and orientation of each dipole superimposed on the subject's own MR images. Both the location and orientation of the dipoles in the parasyylvian region

and time course of the activity are similar between the on- and off-responses.

Figure 7. Scheme of auditory stimulation. A; auditory stimuli consisted of a 1000-Hz pure tone of long duration and two trains of brief pure tone 25 ms in duration. B; the three stimuli were presented randomly at an inter-trial interval (ITI) and a stimulus duration of 3-5 s.

Figure 8. Magnetic fields evoked by the onset and offset of auditory stimulation. Data from a representative subject. A, the top view traces all the sensors. In each response pair, the upper trace illustrates the field derivate along the latitude and the lower trace that along the longitude. B, enlarged waveforms of sensors indicated by circles in A.

Figure 9. Source strength as a function of time. A, superimposed waveforms of the activity in the superior temporal gyrus (STG) of ten subjects. B, location and orientation of each dipole in a representative subject superimposed on the subject's own MR images.

Figure 10. Positive correlation of the amplitude of the activity in the STG between on- and off-responses. A correlation coefficient and p value are indicated for each stimulus condition.

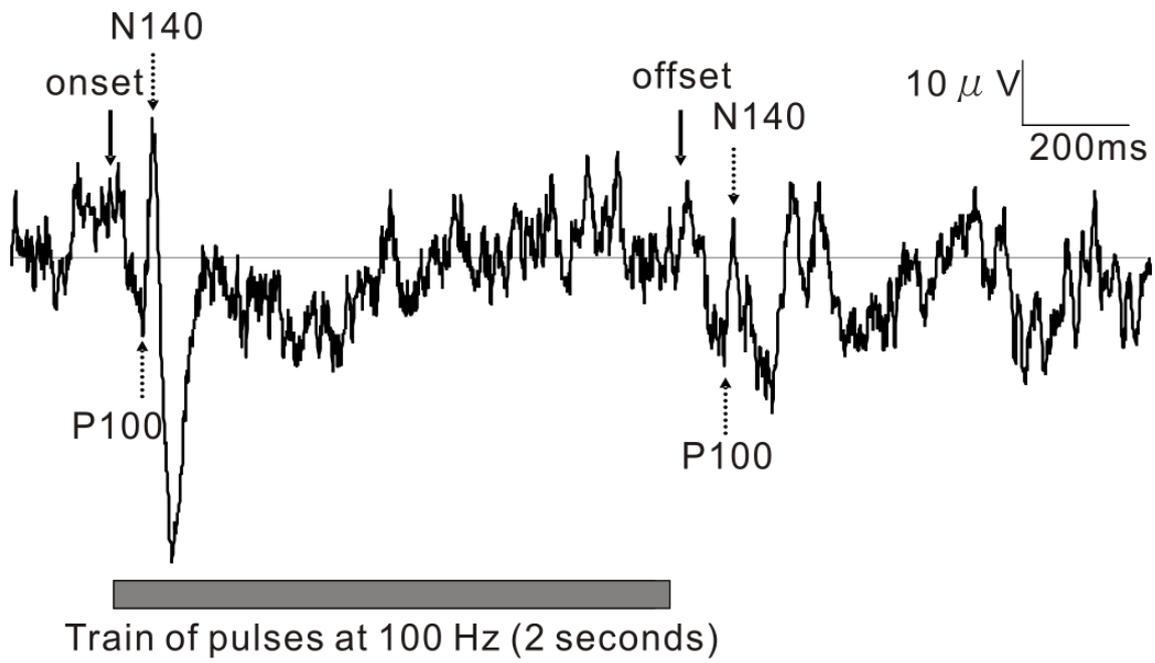


Figure 1

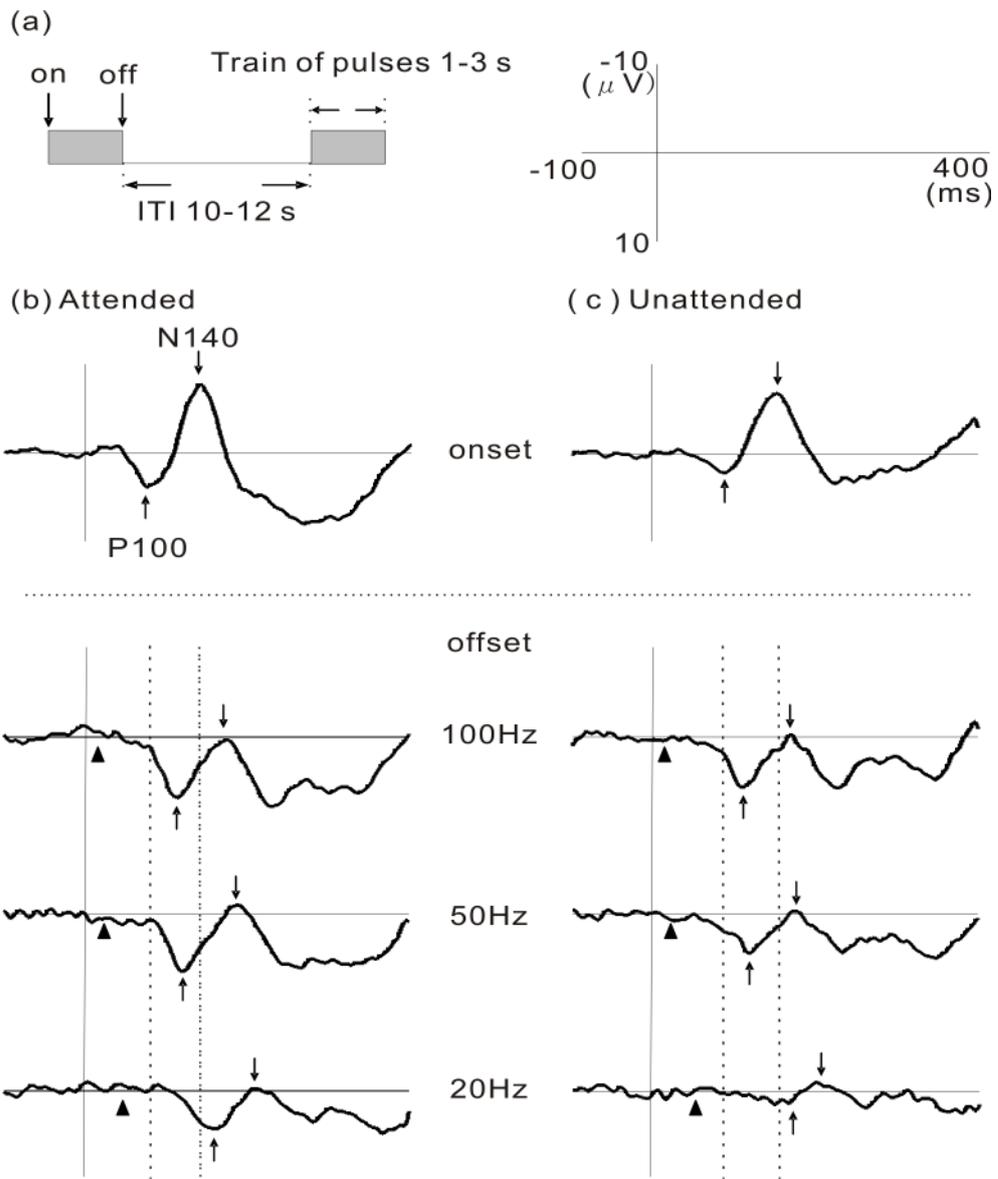


Figure 2

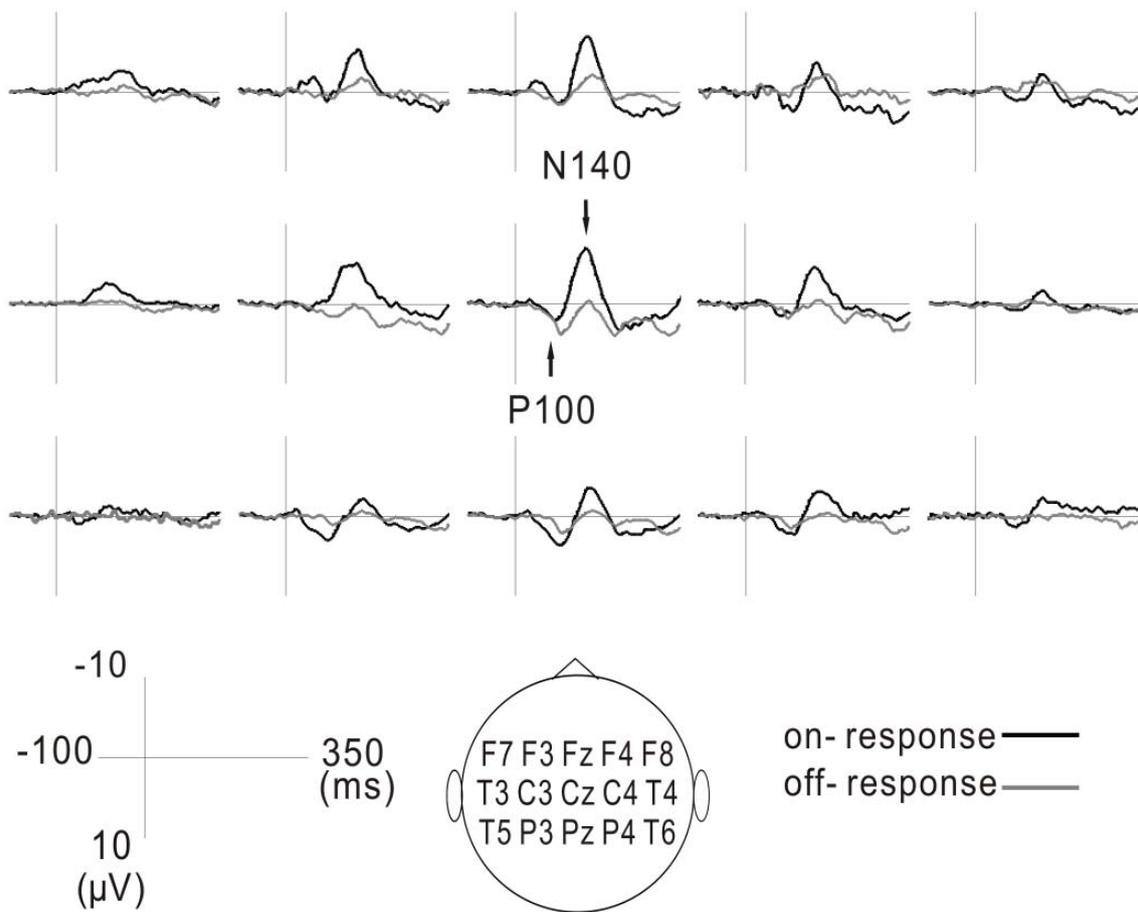


Figure 3

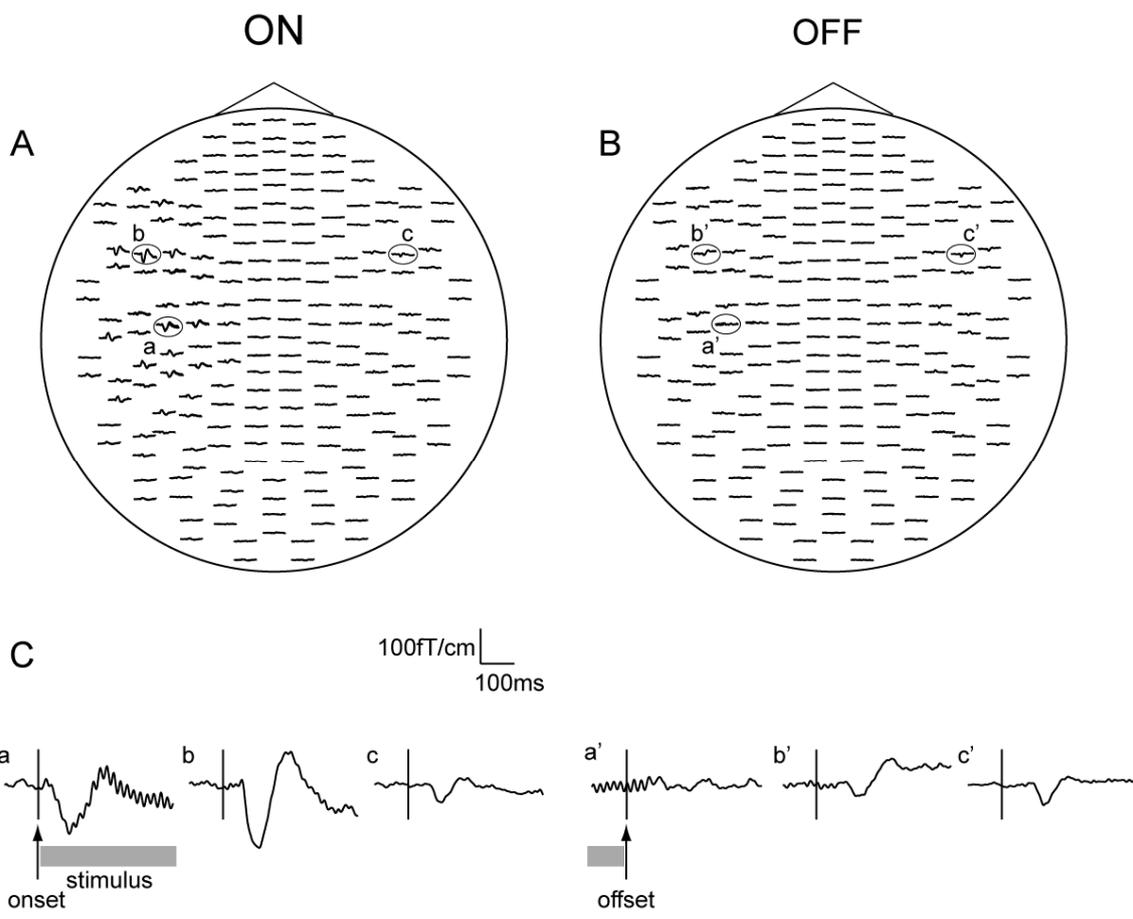


Figure 4

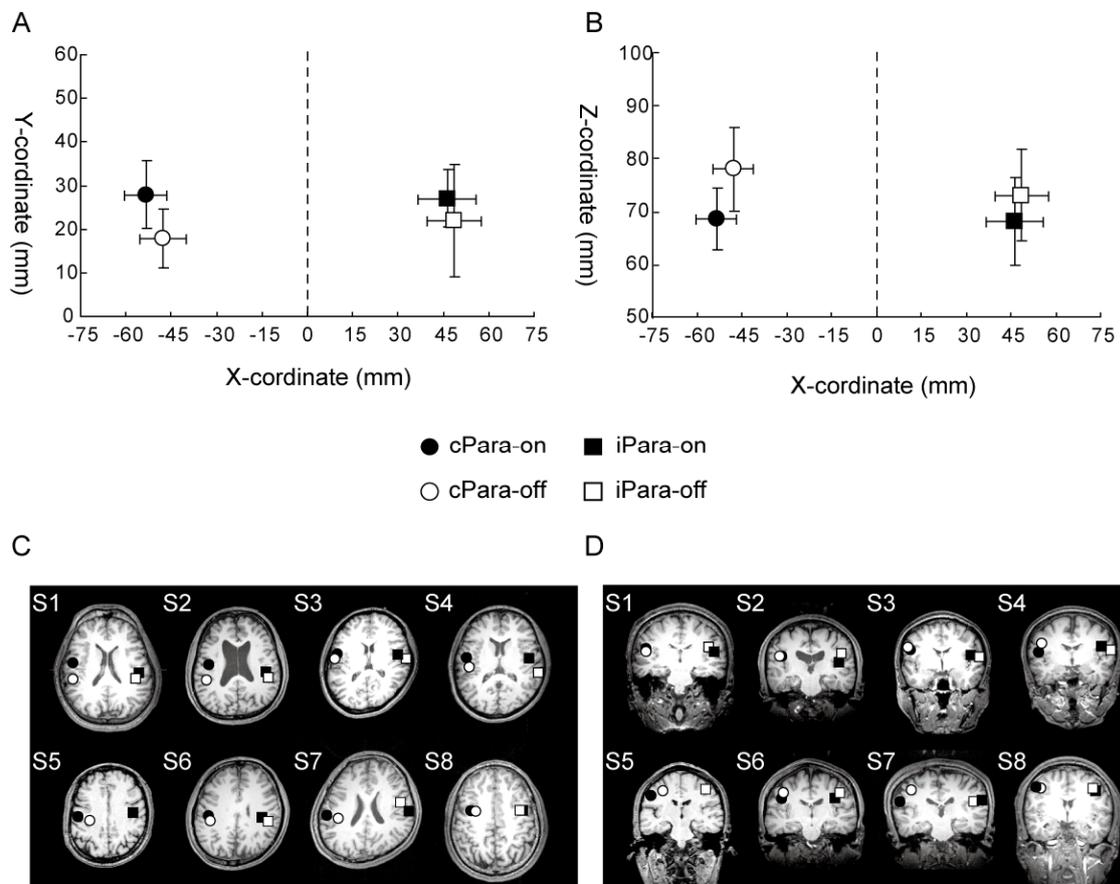


Figure 5

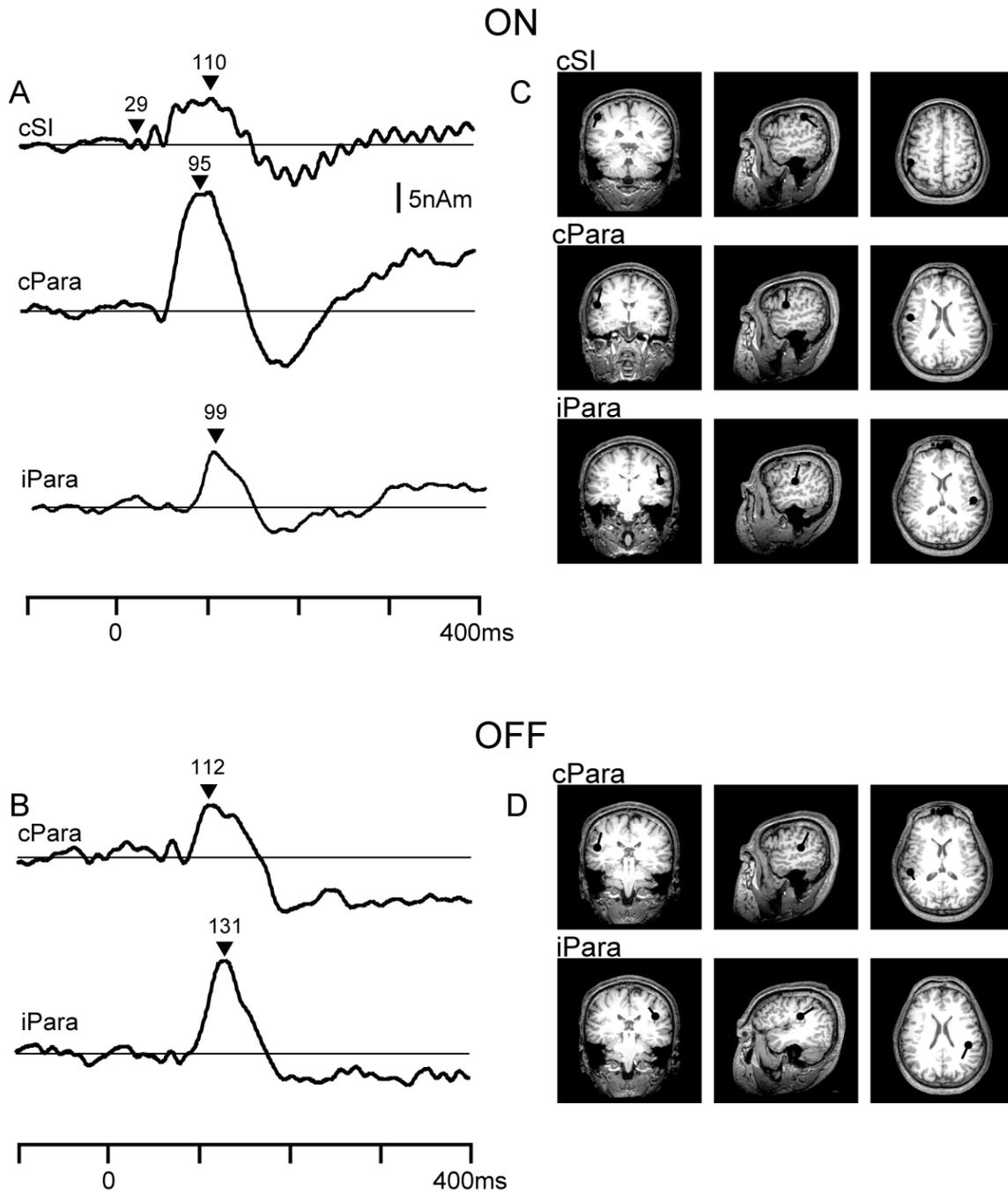


Figure 6

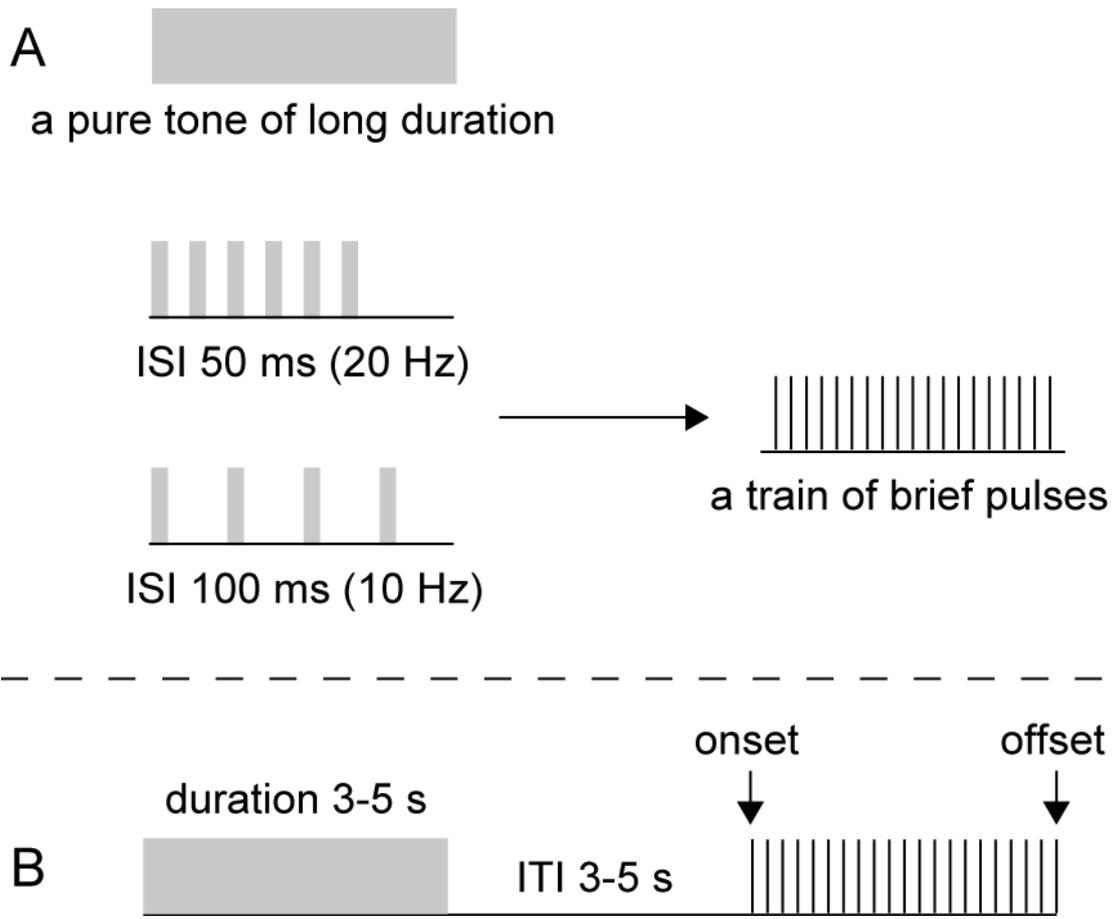


Figure 7

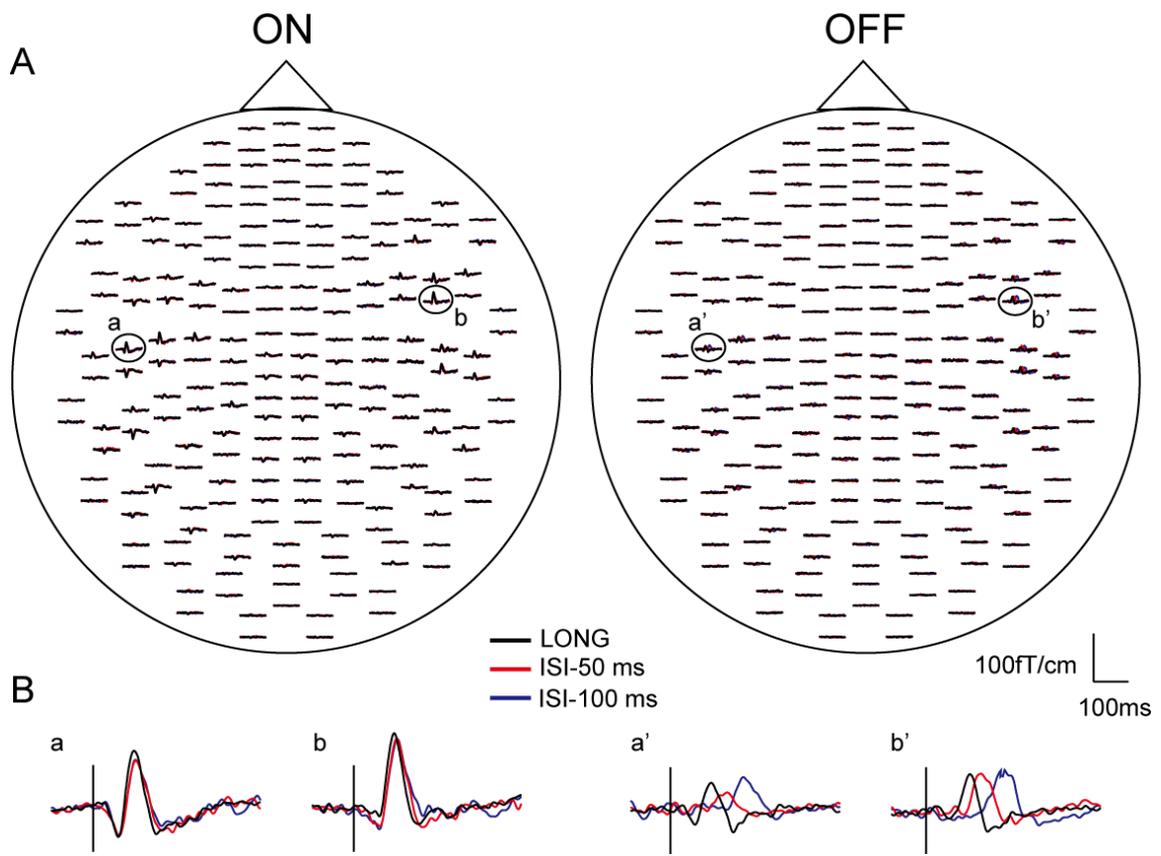


Figure 8

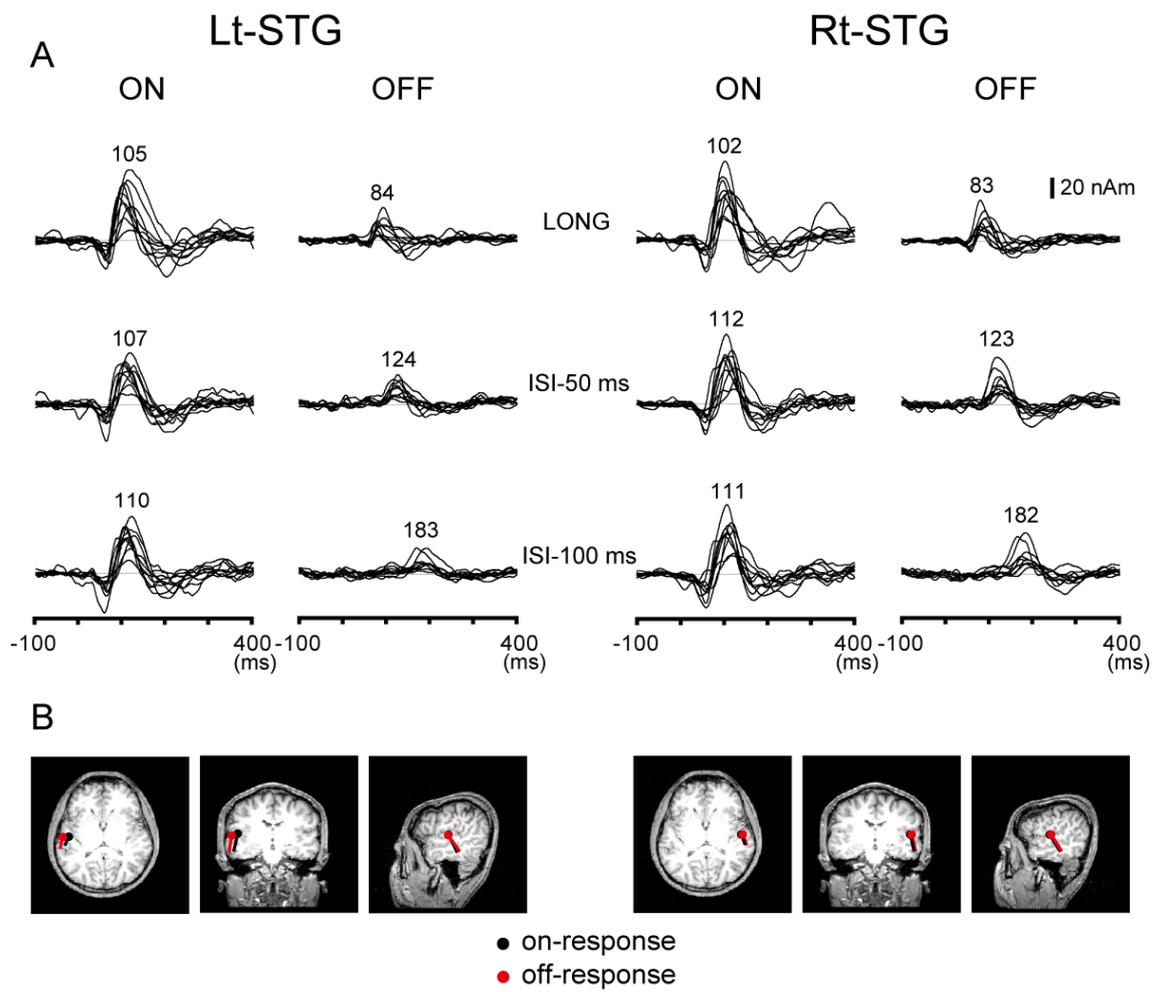


Figure 9

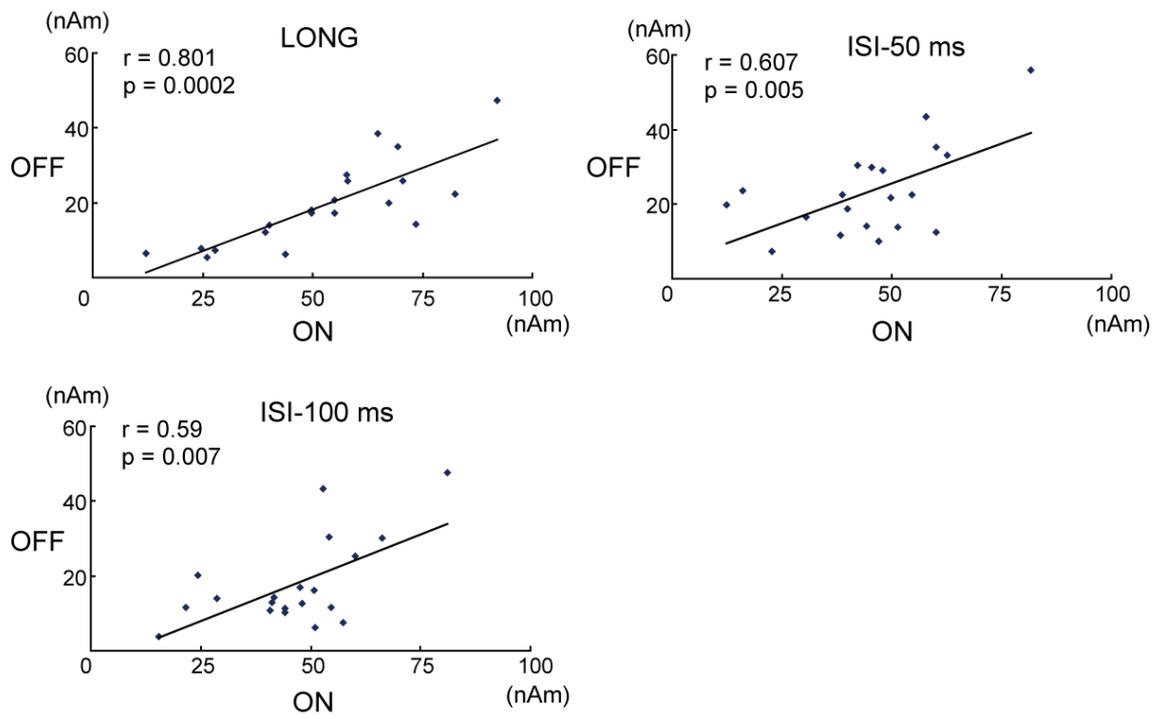


Figure 10