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Research paper

Steady-state MEG responses elicited by a sequence of amplitude-modulated short tones of different carrier frequencies

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ABSTRACT

The auditory steady-state response (ASSR) is a weak potential or magnetic response elicited by periodic acoustic stimuli with a maximum response at about a 40-Hz periodicity. In most previous studies using amplitude-modulated (AM) tones of stimulus sound, long lasting tones of more than 10 s in length were used. However, characteristics of the ASSR elicited by short AM tones have remained unclear. In this study, we examined magnetoencephalographic (MEG) ASSR using a sequence of sinusoidal AM tones of 0.78 s in length with various tone frequencies of 440–990 Hz in about one octave variation. It was found that the amplitude of the ASSR was invariant with tone frequencies when the level of sound pressure was adjusted along an equal-loudness curve. The amplitude also did not depend on the existence of preceding tone or difference in frequency of the preceding tone. When the sound level of AM tones was changed with tone frequencies in the same range of 440–990 Hz, the amplitude of ASSR varied in a proportional manner to the sound level. These characteristics are favorable for the use of ASSR in studying temporal processing of auditory information in the auditory cortex. The lack of adaptation in the ASSR elicited by a sequence of short tones may be ascribed to the neural activity of widely accepted generator of magnetic ASSR in the primary auditory cortex.

1. Introduction

The auditory steady state response (ASSR) of the scalp potential is elicited by repetitive short acoustic stimuli with a maximum response at 35–45 Hz repetition rate (Galambos et al., 1981). Cortical and subcortical origins of the potential ASSR at the thalamus and brainstem have been suggested from cross-modal stimulation (Galambos, 1982), intracranial recording (Lee et al., 1984), patient study (Spydell et al., 1985) and scalp topography (Johnson et al., 1988). The magnetic counterpart of ASSR recorded by MEG (magnetoencephalography) has indicated an auditory cortical generator and has been used to characterize frequency-specific organization of neural activity in the auditory cortex (Romani et al., 1982; Mäkelä and Hari, 1987).

In humans, scalp potential ASSR evoked by a sinusoidal amplitude-modulated (AM) sound has been observed up to a modulation frequency of 400 Hz (Rees et al., 1986). However, the frequency-following response recorded with a subdural electrode from the human auditory cortex showed a steep drop in amplitude above 40 Hz (Lee et al., 1984). Such a difference in auditory responses may be due to the subcortical contribution in the scalp potential. Previous studies using EEG (electroencephalography) and MEG have revealed various aspects of ASSR including the generation mechanism (Pantev et al., 1993; Presacco et al., 2010) and effects of stimulus parameters such as sound level, modulation frequency and carrier frequency (Pantev et al., 1996; Ross et al., 2000; Wienbruch et al., 2006). As for the sound level effect, the amplitude of ASSR increases as the level increases in a logarithmic (dB) manner (Ross et al., 2000), in line with long-latency evoked responses of N1/N1m (Thaerig et al., 2007; Soeta and Nakagawa, 2012), where N1m is the magnetic counterpart of N1 potential. Regarding the dependence of ASSR on carrier frequency, detailed results have been provided by several studies (Pantev et al., 1996; Ross et al., 2000; Wienbruch et al., 2006). As a general trend, the amplitude of ASSR decreases with increase in carrier frequency in the range from about 250 to 4000 Hz, in which the decrease between 500 and 1000 Hz is relatively small. Those results seem to

Abbreviations: AEF, auditory evoked field; AM, amplitude modulation(ed); ANOVA, analysis of variance; ASSR, auditory steady-state response; EEG, electroencephalography; f_c, carrier frequency; f_m, modulation frequency; GOF, goodness of fit; MEG, magnetoencephalography; MR(I), magnetic resonance (imaging); nHL, normal hearing level; SL, sensation level; SPL, sound pressure level.

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depend how the magnitude of sound is controlled in a wide range of frequencies, i.e., whether the sound pressure level (SPL), sensation level (SL) or loudness is kept constant through the carrier frequency. Since SL or loudness is a function of carrier frequency, the effect of stimulus intensity may be mixed in such carrier frequency dependence; the frequency dependence has not been established yet. In most of those studies, repetition of short sound bursts or long-lasting continuous AM sounds typically more than 10 s in length were used.

The ASSR is a clinically useful tool for objective audiometry by evaluating the response threshold (Lins et al., 1996; Picton et al., 2005; Scherf et al., 2006). In such clinical test, delivery of sinusoidal AM tones in a short period while changing the carrier frequencies in an audible range would be a method for fast examination. The ASSR may also be applied in basic studies of temporal processing of input sounds in the auditory cortex. A typical example is the auditory illusion proposed by Deutsch (1974, 1975), in which distinct tonal sequences within about one octave pitch are delivered to the right and left ears. Most listeners hear illusory percepts of smooth contours or stable pitch alternation in the two ears instead of original discontinuous pitch contours. Evoked potential and MEG studies have challenged this phenomenon (Ross et al., 1996; Lamminmäki and Hari, 2000, 2012), but dynamical processes in the right and left auditory cortices underlying the illusion were not clarified. In those studies, the temporal resolution was not sufficient or responses to the right- and left-ear sounds were not separated. In a suitable approach by the ASSR, successive short AM tones with variation in pitch, mimicking the musical tones used in the illusion paradigm, should be used. However, little is known about temporal characteristics of the ASSR elicited by short-sinusoidal AM tones in analyzing the obtained ASSR data in these clinical and basic studies. Specifically, how the amplitude of the ASSR varies when the f_c and/or the sound pressure of the tone are changed from one tone to another in a short time of less than 1 s is a central issue.

Adaptation and transient characteristics by preceding sounds are the key factors that affect the carrier frequency and sound-level dependence of short-tone-elicited ASSR. A behavioral study showed that long exposure to sinusoidal AM stimuli elevated thresholds for detection of subsequent AM sound, where the loss of sensitivity (adaptation) followed a slow asymptotic curve continuing for 20–30 min. In contrast, recovery was rapid, within the first 60 s (Tansley and Suffield, 1983). A neurophysiological study (Bartlett and Wang, 2005) using awake marmosets indicated that about 60% of tested units in the auditory cortex showed significant suppression of firing rate to the second AM sound in a stimulus sequence consisting of two sinusoidal AM sounds. This suppression lasted for more than 1 s. The suppression was often tuned such that the preceding sound whose parameters were similar to the succeeding sound produced the strongest suppression. To our knowledge, corresponding experiments of human ASSR using a sequence of similar/distinct sinusoidal AM sounds have not been reported. For a repetition of pulse AM sounds, it was shown that amplitude of the ASSR of MEG was dependent on the temporal structure of the stimulus sounds, i.e., modulation waveform, even when the amplitude of the wave and spectral properties were kept the same (Simpson et al., 2012). In that experiment, AM sounds of a constant carrier frequency were shaped to be a sequence of short-width pulses at 4 Hz repetition rate. The 4 Hz component of the ASSR was larger when different widths of the AM pulses were variably mixed than when the pulse width was constant. This result suggests a certain effect of temporal structure of AM sound on the adaptation of ASSR. Regarding the transient characteristics, Ross et al. (2005) reported that the amplitude of the ASSR of MEG recovered to its original height in a period of 200–250 ms when the ASSR to continuous AM tone was depressed by desynchronization due to noise-burst perturbation. The recovery form and the time resembled those after initiation of the stimulus sound. Such transient depression and recovery of the ASSR may also be expected at the boundary of frequency change of AM tones, if present, through the variation of the phase of ASSR with the carrier frequency (Ross et al., 2000).

The ASSR measured with MEG shows exclusively the activity of the auditory cortex. Localization of the source of magnetic ASSR on anatomical MR images (Pantev et al., 1996; Engelien et al., 2000; Herdman et al., 2002; Steinmann and Gutschalk, 2011) has consistently indicated a single dipole in the primary auditory cortex, which is known to be located in the medial part of Heschl's gyrus in the superior temporal plane (Galaburda and Sanides, 1980; Hackett et al., 2001; Fullerton and Pandya, 2007). The latency of ASSR, if converted from 40-Hz repetition rate, corresponds to that of the middle latency response. The middle latency responses measured using MEG consisted of three waves having short rise and fall times of 5–10 ms in a period of about 40 ms after the click stimulation (Kuriki et al., 1995). Dipole sources of those waves were located in the medial site of the auditory cortex. This result supports the view that the ASSR originates in the primary auditory cortex.

In contrast to the results of ASSR studies, it is widely accepted that long-latency evoked responses of N1/N1m exhibit strong adaptation in repeated stimulation of sounds in a manner that is frequency-specific, i.e., the response reduction is stronger when the frequency components of preceding sound are closer to those of succeeding sound (Näätänen et al., 1988; Nishimura et al., 2004). The decrement depends on the repetition rate of sinusoidal tone bursts; the amplitude reduction of N1/N1m is larger for shorter inter-stimulus intervals (Budd et al., 1998; Rosburg et al., 2010). The peak amplitudes of N1/N1m/P2m become constant after the first reduction at the second stimulus in repeated stimulation of pure tones and complex tones comprising higher harmonics. This result was interpreted to show the refractory effects of populational neurons rather than habituation (Kuriki et al., 2006; Rosburg et al., 2010). Regarding the frequency dependence, the amplitude/moment of N1m is lower at higher frequencies for pure tone stimulation. It is estimated to be almost independent in a range lower than 1 kHz (Gabriel et al., 2004).

From the aforementioned previous results about ASSR on the behavioral adaptation by long exposure to AM sound, amplitude suppression by dissimilar temporal waveforms, short recovery from desynchronization, and the primary auditory cortical genesis, we hypothesize that the ASSR, especially that of MEG, evoked by sinusoidal AM tones was not attenuated by the change in stimulus parameters of the preceding tone, such as sound level and carrier frequency provided that the length of the AM tone is longer than the recovery time. This may hold even when the AM tones are connected in series with other AM tones having different carrier frequencies and sound levels. The aim of this study was to clarify the basic characteristics of the ASSR elicited by sequential short AM tones having a length of less than 1 s. We examined how the magnitude of ASSR of MEG depended on the carrier frequency and the level of sinusoidal AM sound with a preceding adjacent tone while the modulation frequency was fixed to about 40 Hz. The range of carrier frequencies was restricted to about one octave considering application to basic study of the auditory illusion, in which high spatial resolution of MEG is expected to enable separate detection of activities in the right and left auditory cortices. We measured the amplitude of ASSR in response to paired and consecutive AM tones varying in carrier frequency or sound pressure, in comparison with the corresponding transient evoked response of N1m. Analysis of a single dipole source was also carried

out to confirm the location of the generator of the short-tone ASSR and to evaluate the observed effects in terms of the strength of neural activity, i.e., dipole moment.

2. Materials and methods

During the course of this study, we performed two separate experiments (Exp. I and Exp. II). The objective of the first experiment was to examine the effects of carrier frequency and its change on ASSR in a range of about one octave in continuing stimulation of short AM tones. The second experiment was carried out three months after the completion of Exp. I. Based on the main results obtained in Exp. I showing that the effect of carrier frequency on the amplitude of ASSR was nonsignificant, Exp. II was carried out to determine the effect of sound pressure within the same range of carrier frequencies.

2.1. Subjects

2.1.1. Experiment I

Ten male subjects with a mean age (SD) of 22.5 (1.03) years participated. They were all right-handed except one subject.

2.1.2. Experiment II

Nine male subjects and one female subject with a mean age (SD) of 23.9 (4.75) years participated in the second experiment. They were all right-handed. The subjects in the Exp. I and Exp. II gave written informed consent following procedures approved by the ethics committee of Tokyo Denki University.

2.2. Stimuli

2.2.1. Experiment I

The stimulus sound was a pair of amplitude-modulated (AM) tones of 780 ms in length having different carrier frequencies (f_{c1} and f_{c2}) connected without intermission (Fig. 1a). The modulation frequency (f_m) was 41.0256 Hz and the modulation depth was 100%. The 780-ms length of each f_c-tone included 32 cycles of modulated waves, where transition of the f_c change occurred at the time of zero amplitude.

We prepared stimulus sounds of four pairs of f_{c1}/f_{c2} of 440/990, 550/440, 880/990 and 990/440 Hz. These pairs could be divided by the first tone into groups of low f_c (440 and 550 Hz) and high f_c (880 and 990 Hz) and by the second tone into groups of small f_c change (440 and 990 Hz following 550 and 880 Hz, respectively) and large f_c change (440 and 990 Hz following 990 and 440 Hz, respectively). Sound signals of the four f_{c1}/f_{c2} combinations were generated with a PC at a sampling frequency of 44.1 kHz and mixed with inter-stimulus intervals of 780 ms to form a quasi-random sequence, which included 4 sets of f_{c1}/f_{c2} (440/990, 550/440, 880/990 and 990/440 Hz) pairs, i.e., 16 epochs of the pair in total. A measurement run of MEG recording consisted of the delivery of this stimuli sequence. Each subject underwent 50 measurement runs in about 35 min. Thus, responses of 200 epochs of each fc_1/fc_2 pair were obtained.

The sound pressure level (SPL) of the AM tones was measured with a sound meter at the earpiece of the sound delivery system. The SPLs of different f_c tones were adjusted by controlling the amplitude of the sound signal to follow the equal loudness curve (ISO 226:2003), where the SPL at 440 Hz was set to be 70 dB (Fig. 1b).

2.2.2. Experiment II

The stimulus sound was a sequence of AM tones of six f_cs of 440, 550, 660, 770, 880 and 990 Hz, each with a length of 780 ms,

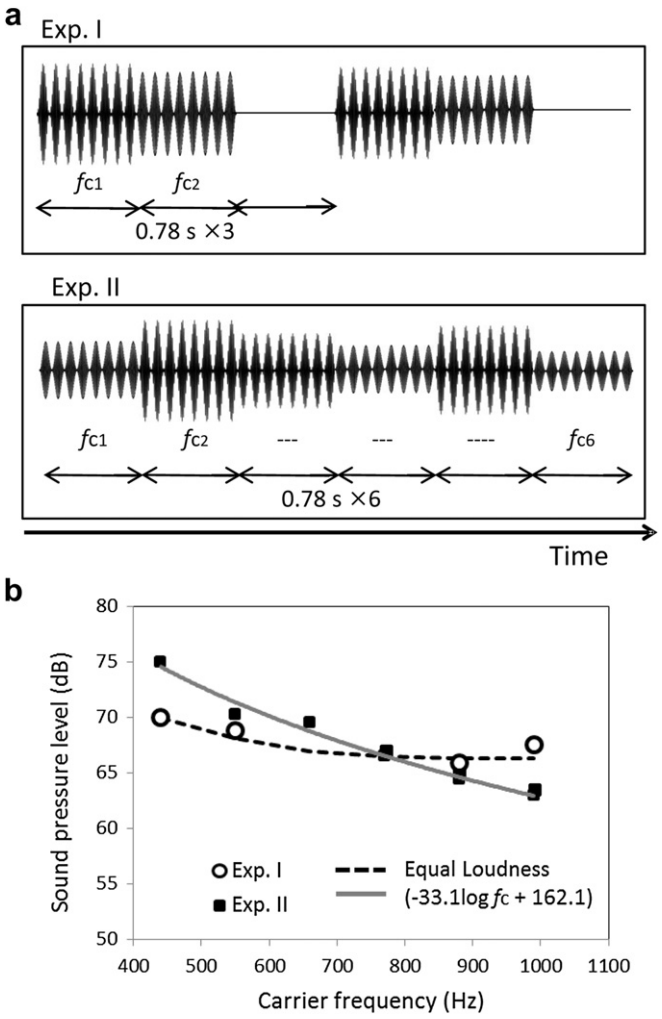

Fig. 1. (a) Waveform of sound signal and time chart of sound presentation. In Exp. I, stimulus sound was a pair of amplitude-modulated (AM) tones of 780 ms in length having different carrier frequencies (f_{c1} and f_{c2}) connected without intermission. The paired AM tones of different combinations of f_{c1}/f_{c2} were mixed with 780-ms intervals to form a continuous stimulus sequence. In Exp. II, AM tones of 780 ms in length having six carrier frequencies (f_{ci}) between 440 and 990 Hz were mixed and connected without intermission to form a stimulus sequence. (b) Sound pressure level (SPL) of AM tones of stimulus sounds adjusted and measured at the earpiece of a sound delivery system. In Exp. I, AM tones of four carrier frequencies composing f_{c1} and f_{c2} had SPLs close to an equal loudness curve. In Exp. II, the SPL of AM tones of six f_{ci} had a slope being higher at lower frequencies. This dependency is approximated by a logarithmic form indicated by a solid line.

connected without intermission (see Fig. 1a). The modulation frequency f_m was 41.0256, which ensured that the boundary between different f_c-tones occurred at zero amplitude, at a modulation depth of 100%. From random sequences of the six frequencies generated with a PC in many trials, we selected two tone-sequences of A (770/440/660/880/550/990 Hz) and B (770/990/550/880/660/440 Hz) that had smallest standard deviations (SD) of the frequency difference (in absolute value) across adjacent tones. Then A and B sequences were mixed and connected in quasi-random order to form a stimuli series (A/B/A/A/B/A/B/B/A/B), including 5 sequences of A and B. The mean and SD of the frequency difference (Δf_c) across all f_c boundaries within this series were 293 and 90 Hz, respectively. We expected that effects of Δf_c in the preceding tones on ASSR would be minimal by using such Δf_c-controlled tone sequences, though the effect of Δf_c was found to be nonsignificant in the paired tones in Exp. I. This stimuli series was presented repeatedly 20

times in MEG recordings lasting for about 16 min. Thus, responses of 100 epochs of each f_c tone were obtained for each of the A and B sequences.

The SPL of the stimulus tones was adjusted to be higher at lower f_c and lower at higher f_c across the equal loudness curve of Exp. I (see Fig. 1b). This adjustment was performed in a procedure that included measurement of SPL of the stimulus sound with a sound level meter at the earpiece of the sound delivery system, calibration of the amplitude of the sound signal generated by the PC, and changing the amplitude of the sound signals of different f_cs to follow the desired SPL versus f_c curve. The obtained SPLs were approximated by a logarithmic form of $\mathrm{SPL(dB)} = \alpha \log f_c + \text{constant}$ (Fig. 1b), where the coefficient α was −33.1, and the constant was 162.1. The values of SPL were 75 and 63 dB at the lowest (440 Hz) and highest (990 Hz) f_c, respectively.

2.3. Measurements

2.3.1. Experiments I and II

MEG recordings were performed using a whole-head system (Elekta, Neuromag, Finland) in a magnetically shielded room. The system had a total of 122 sensors detecting orthogonal field gradients of $\partial Bz/\partial x$ (X-channel) and $\partial Bz/\partial y$ (Y-channel) at 61 locations over the whole head, where the magnitude of the field gradient is given by $\{(\partial Bz/\partial x)^2 + (\partial Bz/\partial y)^2\}^{1/2}$. The stimulus sound was presented to the left ear of each subject through a plastic tube and an earpiece, while an earplug was inserted in the right ear. The measurement condition was passive listening. Subjects were instructed to simply listen, not intentionally, to the sound with their eyes open. Arousal was monitored with a video camera installed in the shielded room. It was confirmed that the subjects kept their eyes open during the recording period. The measured MEG signals were filtered to 0.03–100 Hz and sampled at 600 Hz. Signals exceeding 3 pT of amplitude contaminated with artifacts were rejected online on epoch basis (Exp. I) or sequence basis (Exp. II). It was found during the period of Exp. II that one or two pairs of X- and Y-sensors in the temporal area were noisy with an elevated white noise level. Manipulation of control parameters of the sensors did not improve the noise. The data of these noisy sensor channels were deleted in the subsequent processing in Exp. II.

2.4. Data processing and analysis

2.4.1. Experiment I

Recorded MEG signals were averaged offline across 200 epochs selectively for each of the different f_{c1}/f_{c2} pairs (440/990, 550/440, 880/990, 990/440 Hz) with the aid of a trigger time-locked at the beginning of the pair. The averaged epochs were filtered to 30–50 Hz to reduce low and high frequency noises and then wavelet-transformed using the Morlet mother-wavelet function of a width of 14. This value of the width had been determined in a simulation study using sinusoidal waves. Under this condition, the time resolution, i.e., rise and fall time of the sinusoidal wave, was 130 ms, and the frequency resolution (half width) was 8 Hz. Here, the time resolution was a necessary condition to observe transient behavior of the ASSR at the boundary of frequency change. The frequency resolution was reciprocal to the time resolution. From the wavelet-transformed component of 41 Hz, we obtained the amplitude of ASSR as a function of latency.

To reduce the noise further in the spatial domain, a set of X- and Y-channels of the largest MEG signal was selected in the right temporal area of the head, which represents the responses in the contralateral hemisphere to the stimulation side (left ear). Surrounding channel-sets of larger signals were also selected to include a total of 12 channels. The amplitudes of ASSR in six X–Y channel sets of the selected channels were combined to be the magnitude of field gradient by the formula described before, and those magnitudes were averaged. Finally, we obtained ASSR waves for the four f_{c1}/f_{c2} pairs in each subject.

In addition to the ASSR, we analyzed the transient response, specifically on the N1m peak, of the auditory evoked field (AEF). To do this, the recorded MEG signals were filtered to 1–30 Hz. Epoch averaging was performed following the procedure in the ASSR processing, where the baseline was set during a 300-ms period before the onset of stimulus tones. Selection of sensor channels, showing larger amplitude of N1m, and the spatial averaging was also performed. The 12 selected channels were common to those in the ASSR processing in all subjects.

For statistical analysis, we computed the average amplitude of ASSR across latency in a time window of the tone period of 0.78 s. The average amplitude was obtained separately for each of the first and second tone responses of f_{c1}/f_{c2} pairs. The amplitude of the N1m peak for statistics was obtained from the peak value in each subject. Repeated measures three-way ANOVA (analysis of variance) was performed to assess the effects of order of response, f_c, and f_c-difference for ASSR and N1m.

2.4.2. Experiment II

The recorded MEG signals were averaged offline across 100 stimuli series separately for A and B sequences using a trigger time-locked at the beginning of each of A and B sequences. The averaged signals were then separated into the epochs of six f_cs with the latency at 780-ms steps. When the epoch signals of A and B sequences were summed further, we found that its magnitude was reduced from the sum of the magnitudes of the epochs of A and B signals, even when identical-f_c epochs were summed. Here, the magnitude means the envelope in absolute value of the ASSR signal. The reason of this magnitude reduction was not clear. We speculated that there was a latency difference, of orders of sampling-time (up to 2×1.67 ms from A and B sequences), across the time-selected epochs between A and B sequences. The addition of the ASSR signals with such a phase mismatch might have resulted in the magnitude reduction. We therefore processed the epoch signals of A and B sequences separately. The epoch signals were filtered to 30–50 Hz and wavelet-decomposed to obtain the amplitude of the 41 Hz component, by a procedure similar to that in Exp. I. Then the amplitudes of the ASSR wave were averaged across the A and B sequences.

Spatial domain averaging of the ASSR wave was carried out in the same way as that in Exp. I. However, we reduced the number of selected channels surrounding the largest-magnitude channel from 12 in Exp. I to six. This is partly due to the deleted noisy channels in the temporal area. One or two pairs (2–4 channels) were included within the area of the selection of the 12 channels. In addition, it was desirable to obtain higher ASSR amplitude by reducing outer channels having lower amplitudes than the central channels, because the sound pressure levels at high f_cs (880 and 990 Hz) were reduced to be lower than those in Exp. I. After this spatial-averaging, we obtained the final form of the ASSR waves for six f_cs from 440 to 990 Hz in each subject. For statistical assessment, the average amplitude of the ASSR wave was computed across latency in a time window of the tone period of 0.78 s.

To obtain the AEF including N1m response, the recorded MEG signals were filtered to 1–30 Hz and averaged across 100 stimuli series separately for A and B sequences. During this averaging, AEF signals were separated into the epochs of six f_cs, where a baseline during a 300-ms period before the onset of stimulus tones was used. Then the AEF epochs were combined between A and B sequences and space-averaged across the six selected channels, in the same way as that in the ASSR processing. We obtained the

waveforms of AEF within the tone period for six f_cs from 440 to 990 Hz in each subject.

2.5. Source analysis

2.5.1. Experiment I

Localization of equivalent current dipoles was carried out to obtain and compare the source locations of ASSR signals, which were epoch-averaged and filtered to 40–42 Hz, and N1m signals, which were epoch-averaged and filtered to 1–30 Hz, in different pairs of f_{c1} and f_{c2}. We calculated dipole parameters of (x, y, z) coordinates and the moment (Q) using MEG signals of 30–34 selected channels surrounding the largest-signal channel over the temporal auditory area. The calculations were repeated at latencies of every sampling-time (1.67 ms) step during a tone period of 0.78 s for the ASSR and during a 30-ms period around the N1m peak. Among the calculated dipoles, we selected four dipoles having largest goodness-of-fit (GOF) values in each of the f_{c1} (440, 550, 880 and 990 Hz) and f_{c2} (990, 440, 990 and 440 Hz) conditions. Those dipoles were grouped into low-f_c (440 and 550 Hz) and high-f_c (880 and 990 Hz) of the first and second tones, and the dipole parameters were averaged across the dipoles within each group to improve the accuracy of the parameters. Thus, single dipoles with their coordinates were obtained in the conditions of two f_c-groups of the first and second tones for ASSR and N1m responses in each subject. During this process, we discarded the data from two subjects from our criterion; the mean GOF value within a condition (high f_c/low f_c) did not exceed 80%. As a result, the dipole coordinates were obtained in the full conditions in eight of ten subjects, who were common in ASSR and N1m. Repeated measures three-way ANOVA (analysis of variance) with the factors of response (ASSR/N1m), order of the response (first/second) and f_c (low/high) was performed to assess the source locations of ASSR/N1m and the effects of preceding tone and tone frequency.

2.5.2. Experiment II

In this experiment, we performed source localization of ASSR to obtain the time course of the strength of source in the 0.78-s tone period, for comparison with the time course of the amplitude of ASSR for different f_cs. We localized a dipole source at f_c of 440 Hz that had the highest stimulus SPL to represent the source locations in the range of f_c from 440 to 990 Hz. Here, we assumed from previous studies (Pantev et al., 1996; Ross et al., 2000; Wienbruch et al., 2006) that the variation of the source location along the medial–lateral direction, to which the dipole strength is most sensitive, is of the order of 1–3 mm in a change of f_c between about 500 and 1000 Hz (one octave). Under this condition, the source strength estimated with a fixed dipole at 440 Hz was expected to be almost unchanged by the difference in f_c.

Dipole parameters were calculated, using 30–34 selected MEG channels, at latencies of every sampling-time step of 1.67 ms during a tone period of 0.78 s for the 440-Hz epoch of ASSR that was series-averaged and filtered to 40–42 Hz. Considering the lack of signals in a few channel pairs in the temporal area, which might cause an increase in the scatter of calculated parameters, 5–10 dipoles having largest GOF values were selected. The calculated parameters were averaged across the selected dipoles to improve the accuracy. Here, all of the data from two subjects were discarded because of insufficient GOF values (<80%) of dipoles in some f_c conditions. The above processing was performed separately for the stimulus sequences of A and B, and the parameters of the dipoles of A and B sequences were combined into a single dipole source at 440 Hz tone in eight subjects.

Then, assuming the source location at the coordinates of the 440-Hz dipole obtained in each subject, the source strength in units of nAm was calculated in a fixed dipole model as a function of latency during the tone period. In the two subjects who showed insufficient GOF values, mean source coordinates across the other eight subjects were used in the calculation of the source strength. Finally, waveforms of strength of ASSR sources were obtained for different f_cs of 440, 550, 660, 770, 880, 990 Hz in ten subjects.

3. Results

3.1. Experiment I

For qualitative evaluation of the effect of f_c on the ASSR wave, we averaged the ASSR and N1m responses to the paired tones across 880/990 and 990/440 (f_{c1}/f_{c2}) Hz conditions to obtain "high-f_c" first-tone responses and across 440/990 and 550/440 Hz conditions to obtain "low-f_c" first-tone responses. Similarly, for qualitative evaluation of the effect of the difference in carrier frequency Δf_c, we averaged the responses across 990/440 and 440/990 Hz conditions and across 880/990 and 550/440 Hz conditions to obtain "large-Δf_c" (550 Hz) and "small-Δf_c" (110 Hz) second-tone responses, respectively. Those waveforms of ASSR and AEF are shown in Fig. 2a and b, respectively, after grouped by the f_c (left side) and Δf_c (right side). The two curves of the high- and low-f_c ASSRs of the first tone in Fig. 2a were close to each other, suggesting that the amplitude of ASSR did not depend on the f_c. Likewise, close curves of the large- and small-Δf_c ASSRs of the second tone suggest that the amplitude of ASSR did not depend on the Δf_c.

The waveform of ASSR showed a growth of amplitude to its peak at about 340 ms from the onset of AM tone in the first tone response. There was a dip of amplitude at the boundary between the first and second AM tones with a slight delay from the second tone onset. The rise time to the peak of the second tone response was about 300 ms from the onset of the tone.

The waveforms of AFF in Fig. 2b showed a clear N1m peak of the first tone response and the N1m peak superimposed on an elevated baseline, i.e., sustained field, of the second tone response. Close amplitudes of the first N1m peak for high- and low-f_c responses suggest that N1m did not depend on the f_c. In contrast, an obvious difference of the second N1m peak for large-Δf_c and small-Δf_c responses suggests that N1m was reduced by the existence of the preceding tone having a close f_c. Comparison of the amplitudes of responses in Fig. 2a and b indicates that the amplitude of ASSR was order of magnitude smaller than the N1m peak.

The average amplitude of ASSR is shown in Fig. 3a, as the grand mean values across ten subjects, for different tone pairs of f_{c1} and f_{c2}. Here, the average amplitude was obtained by averaging the waveform of ASSR across latency within the time window of the first and second tone periods. Letters "LO" and "HI" in the first-tone bars mean "Low-f_c" and "High-f_c", and letters "LA" and "SM" in the second-tone bars mean "Large-Δf_c" and "Small-Δf_c". They are common to those used in Fig. 2, together with the colors. Three-way ANOVA ($n = 10$) with factors of order, f_c and Δf_c revealed that none of the main effects of those factors were significant (order: $F_{(1,9)} = 2.00$, $p = 0.19$; f_c: $F_{(1,9)} = 0.33$, $p = 0.58$; Δf_c: $F_{(1,9)} = 0.04$, $p = 0.85$), and there were also no significant interactions between the factors. These results indicate that the amplitude of ASSR did not depend on the preceding tone, i.e., the existence, f_c or Δf_c of the adjacent tone.

Fig. 3b shows the grand mean values across ten subjects of the peak amplitude of N1m. These mean values showed marked reduction of the peak amplitude of the second-tone response, which was evaluated after taking a baseline during a prestimulus period of 300 ms to subtract the sustained field. Three-way ANOVA ($n = 10$) with factors of order, f_c and Δf_c revealed that the main effect of the order of response was significant ($F_{(1,9)} = 28.8$,

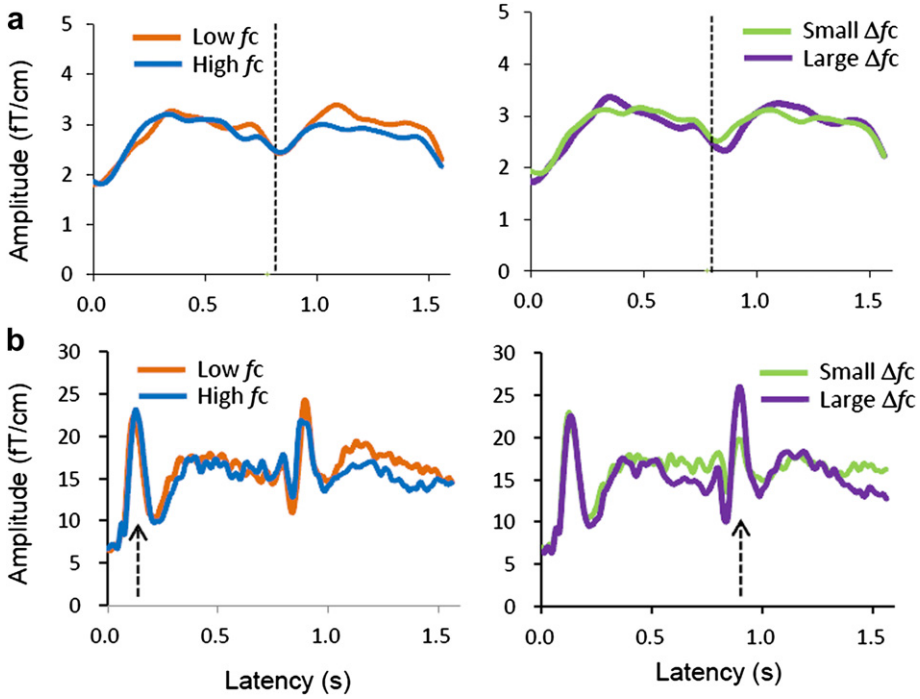

Fig. 2. Grand-mean waveforms of (a) ASSR and (b) AEF across ten subjects, where vertical dotted lines and dotted arrows indicate the onset of the second AM tone of stimulus sound and N1m peak, respectively. These ASSR and AEF were grouped in high (880 and 990 Hz) and low (440 and 550 Hz) carrier frequencies of the first AM-tone (left-side figures) and in large (550 Hz) and small (110 Hz) differences of the carrier frequency of the second AM-tone (right-side figures).

$p = 0.0005$), indicating that the first-tone response was significantly larger than the second-tone response. The main effect of the f_c was not significant ($F_{(1, 9)} = 1.41$, $p = 0.265$), which is compatible with almost invariant amplitude of N1m with frequency inferred at frequencies below 1 kHz (Gabriel et al., 2004). The main effect of the Δf_c was significant ($F_{(1,9)} = 13.8$, $p = 0.0048$) with an interaction with the order ($F_{(1, 9)} = 16.38$, $p = 0.003$). We performed post-hoc paired-t tests across different $\Delta f_c/f_c$ conditions (Bonferroni-corrected for multiple comparisons) and found that, for the second tones, LA 440/990 was significantly larger than SM 550/440 ($p = 0.033$) and SM 880/990 ($p = 0.013$), and that LA 990/440 was significantly larger than SM 550/440 ($p = 0.021$) but not larger than SM 880/990. For the first tones, no significant differences were found. These results of ANOVA and post-hoc tests indicate strong adaptation of N1m, i.e., attenuation of the peak amplitude in the second-tone response, by the first tone having a close frequency. This is in line with the known frequency-specific adaptation of N1/N1m responses (for example, Näätänen et al., 1988; Nishimura et al., 2004).

3.2. Experiment II

Waveforms of the grand-mean ASSR and AEF across ten subjects are shown in Fig. 4a and b, respectively, for different f_cs of AM tones, where the ASSR and AEF waves were the average across stimuli of A and B sequences. General features of the waveform of ASSR are common to those of the second-tone response (Fig. 2a). The initial dip of amplitude was observed at 85 ms after the onset of f_c change at 0 ms. The peak of amplitude occurred at about 300 ms after the onset. Although the waveforms had fluctuations by superimposed noise that remained after averaging the signals across stimuli sequences, a trend of reduction in amplitude with increasing f_c was observed, which is in line with the manipulated variation of SPL with f_c of AM tones. The waveform of AEF showed a prominent N1m peak. The variation of the peak amplitude of N1m with f_c was less clear than that of ASSR.

The waveform of ASSR was averaged across latency during the tone period of 0–780 ms to represent the average amplitude of the response. Fig. 5 shows the grand-mean average amplitude of ASSR across ten subjects (solid circles), where the SPL of stimulus sounds is also shown for comparison. A very proximate relation between ASSR and SPL was obtained. Assuming the invariance of the amplitude of ASSR with f_c and its difference Δf_c observed in Exp. I, we calculated the correlation coefficient (γ) with the SPL and obtained a high coefficient of $\gamma = 0.980$. The significance level using the t-test (two-tailed) was $p < 0.001$ ($t_{(4)} = 9.85$). The amplitude of ASSR was also highly correlated with the difference of SPL (dB) from the equal loudness curve to be $\gamma = 0.960$, with $p < 0.003$ ($t_{(4)} = 6.86$). An approximation curve of the amplitude of ASSR (not shown in Fig. 5) had a logarithmic dependence on f_c, coinciding with the curve of stimulus sounds in Fig. 1b.

The grand-mean amplitude of the N1m peak as a function of f_c is also shown in Fig. 5 (open circles). It is quite dissimilar to the amplitude of ASSR. The results of Exp. I indicated a significant effect of Δf_c but not f_c on the peak amplitude of N1m. In this experiment, Δf_c was controlled in the stimulus sequences of A and B to have the smallest standard deviation (mean Δf_c of 293 Hz). Thus, the main factors that may affect the N1m amplitude are the sound level (SPL) and its difference (ΔSPL) from the preceding tone. The calculation of the correlation coefficients showed that neither γ of SPL nor that of ΔSPL was significant: $\gamma(\text{SPL}) = 0.438$ and $\gamma(\Delta\text{SPL}) = -0.508$.

3.3. Source analysis

Results of the localization of single current dipoles in Exp. I are shown in Fig. 6, where grand-mean source locations across 8 subjects of the first and second tone responses are indicated for ASSR and N1m. They are plotted in the horizontal plane (Fig. 6 left)

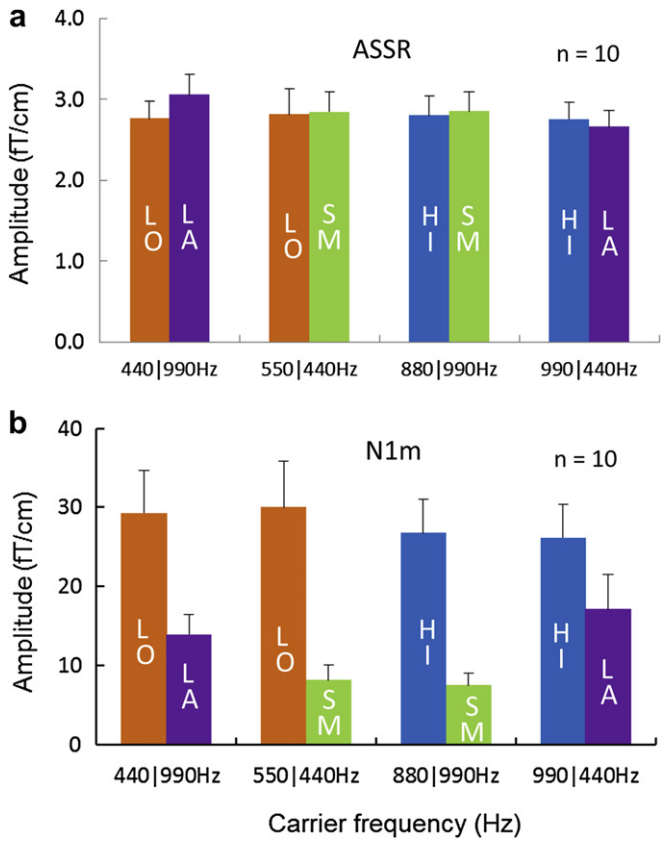

Fig. 3. Grand-mean values across ten subjects of the amplitude of (a) ASSR and (b) N1m for four combinations of paired AM tones with different carrier frequencies (f_{c1}/f_{c2}). Thin vertical bars indicate SE of the mean. Letters "LO" and "HI" in the first-tone bars mean "Low-f_c" and "High-f_c", and letters "LA" and "SM" in the second-tone bars mean "Large-Δf_c" and "Small-Δf_c". They are common to those used in Fig. 2, together with the colors. Note that the amplitude of ASSR had been obtained by averaging the waveform of ASSR across latency within the time period of AM tone and the amplitude of N1m from the height of the N1m peak identified in each subject.

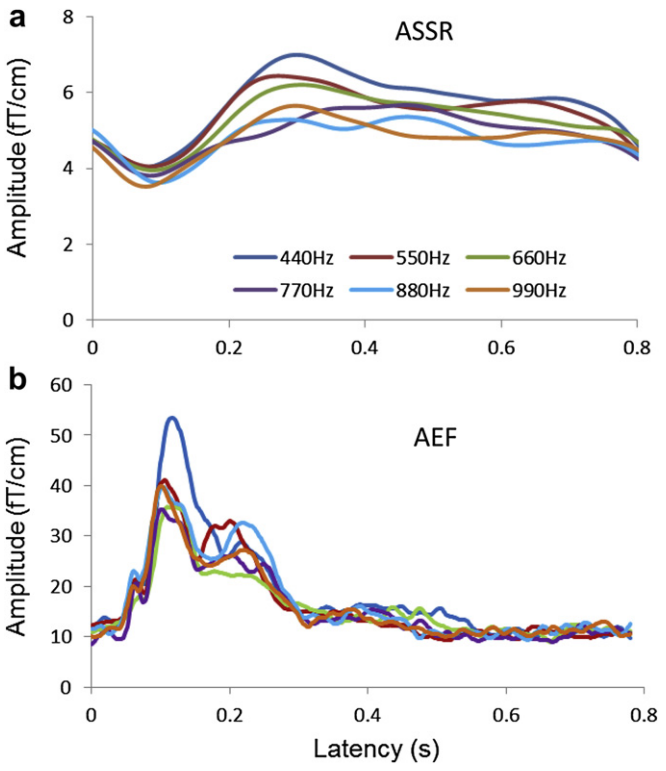

Fig. 4. Waveforms of the grand-mean (a) ASSR and (b) AEF across ten subjects for different carrier frequencies of AM tones. The carrier frequencies are differentiated with colors, as shown under the waveforms of ASSR.

with the *X*-coordinate (medial to lateral direction) and *Y*-coordinate (posterior to anterior direction), in which all of the mean sources were confined to a small area of about 1 cm by 1 cm. The source locations of one subject are superposed on an axial MR image of the same subject (Fig. 6 right). The dipole sources on the MR image indicate that the ASSR sources in this subject were located in the central part of Heschl's gyrus in the auditory cortex. N1m sources were also found in Heschl's gyrus but slightly lateral to the ASSR sources. Results of three-way ANOVA ($n = 8$) with factors of response, order and f_c for the *X*-coordinate revealed a significant main effect of response ($F_{(1,\ 7)} = 10.60$, $p = 0.014$), indicating that ASSR sources were medial to N1m sources. The mean separation was about 5 mm. The main effect of order (first tone/second tone) was significant ($F_{(1,\ 7)} = 5.45$, $p = 0.039$), indicating that the second tone sources were medial (about 3.5 mm) to the first tone sources. While the main effect of f_c (low f_c/high f_c) was not significant, an interaction with order was found ($F_{(1,7)} = 10.45$, $p = 0.014$). Post hoc paired-*t* tests revealed that for the first tone ASSR the high-f_c source was medial to the low-f_c source ($p = 0.006$), but that for the first tone N1m there was no significant difference between the low- and high-f_c sources. For the second tone ASSR and N1m, there were no significant differences. Here, the difference in the *X* coordinate of the second-tone ASSR sources was about 5 mm. This value and its direction in the medial–lateral axis are compatible with the "tonotopic organization" of ASSR showing a medial shift of 1–3 mm/octave in about 500–1000 Hz, reported previously (Pantev et al., 1996; Ross et al., 2000; Wienbruch et al., 2006). For the *Y*-coordinate, three-way ANOVA revealed a significant main effect of order ($F_{(1,7)} = 6.22$, $p = 0.041$) with no significant interactions, where the second tone sources of N1m and ASSR were, respectively, about 4 mm and 1 mm anterior to the first tone sources. No significant main effects of response and f_c were found. For the *Z*-coordinate, there were no significant main effects of response, order and f_c or their interactions.

Waveforms of the grand-mean source strength of the dipole moment across ten subjects obtained in Exp. II are shown in Fig. 7 for different f_c tones. The general trend of waveforms showing an initial dip and a broad maximum followed by gradual decrease was common to that of the amplitude of ASSR (Fig. 4a), but the waveforms were blurred throughout the latency. Such obscuring was probably caused by inaccuracy of the estimation of dipole parameters from low-amplitude ASSR responses. Nevertheless, when the moment in the waveform was averaged over the latency during the stimulus period, it was found that its dependence on the f_c was very close to that of the average amplitude of ASSR (Fig. 8). A high correlation coefficient of 0.981 ($t_{(4)} = 10.21$, $p < 0.001$) was obtained between the amplitude in fT/cm and the moment in nAm. Such agreement suggests that the magnitude of the signal and that of the source can be quantitative measures of ASSR. There seemed to be a difference, however, in the magnitude of error bars between the amplitude and the moment. For quantitative evaluation of this difference, we normalized the standard deviations across subjects of the amplitude and the moment by their mean values, i.e., (SD/Mean), for the six f_cs. The paired *t*-test (two-tailed) showed that this normalized SD was significantly larger in the moment than in the amplitude ($t_{(5)} = 8.64$, $p = 0.0003$). This result indicates that the amplitude of the MEG signal is more accurate than the source strength in short-tone evoked ASSR, when the signal-to-noise ratio is not sufficiently high to make accurate dipole estimation.

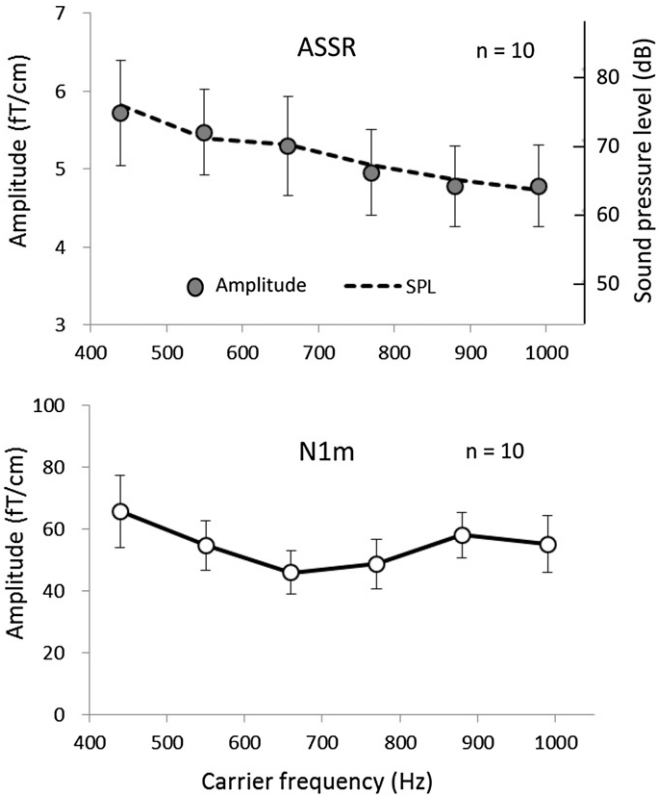

Fig. 5. Grand-mean amplitudes of ASSR (solid circles) and N1m peak (open circles) across ten subjects for various carrier frequencies. Bars indicate SE of the mean. Sound pressure level (SPL) of stimulus AM tones is compared with the amplitude of ASSR, where only a line connecting the SPL values is shown for clarity. The amplitude of ASSR had been obtained by averaging the waveform of ASSR across latency within the time period of AM tone and the amplitude of N1m from the height of the N1m peak identified in each subject.

4. Discussion

An interesting finding in this study is the absence of adaptation of ASSR in the paired tone stimulation in Exp. I. This is evidenced by the observation that the amplitude of the second-tone response was not significantly reduced from the amplitude of the first-tone response, regardless of the frequency or the frequency difference of the first tone. There was a dip of the amplitude at a latency slightly delayed from the onset of the second tone. The recovery time of the amplitude, after the change in carrier frequency, was about 250 ms from the dip. This transient time was much shorter than the stimulus period of 780 ms. This result is in line with our hypothesis of the invariance of ASSR against the change in the parameter of preceding tone, under the condition that the stimulus tone is longer than the recovery time. The dip structure was also observed in the waveform of ASSR around the boundary of the change in carrier frequency (Exp. II), which resembles the transient decrement of the amplitude of ASSR associated with a discontinuity of the phase of ASSR (Ross et al., 2005). The phase of ASSR depends on the carrier frequency, being advanced by about 40° with its one octave increase (Ross et al., 2000). When the carrier frequency changes temporally, the phase of ASSR follows its contour (Patel and Balaban, 2000). Given these related observations in previous studies, it is conceivable that a phase shift occurred at the boundary of the carrier frequency and that the dip of amplitude was caused by this phase discontinuity.

The absence of adaptation of ASSR is in clear contrast to the peak amplitude of N1m response showing appreciable reduction by the preceding tone having close frequency. In this regard, the mean location of the dipole sources across eight subjects was confined in a narrow area of 1 cm square in the mediolateral–posteroanterior plane for the ASSR and N1m responses of different conditions. The dipole sources in the MR image of one subject indicated a central part of Heschl's gyrus in the auditory cortex. In addition to these, the ASSR sources were located medially to the N1m sources with a significant separation of about 5 mm. These features of anatomical and relative locations of ASSR source are consistent with the results of previous studies suggesting that the MEG source of ASSR exists in the primary auditory area (AI) (Pantev et al., 1996; Engelien et al., 2000; Herdman et al., 2002; Ross et al., 2002; Steinmann and Gutschalk, 2011). It is therefore conceivable that the observed absence of adaptation of ASSR is a consequence of the activity of the primary auditory cortex, subserving low-level processing of auditory information.

It has been proposed that the auditory N1/N1m response in humans consists of early and late subcomponents (Jääskeläinen et al., 2004; Ahveninen et al., 2006). Cortical activities of the early and late components extend, respectively, posteriorly including the planum temporale and anteriorly including

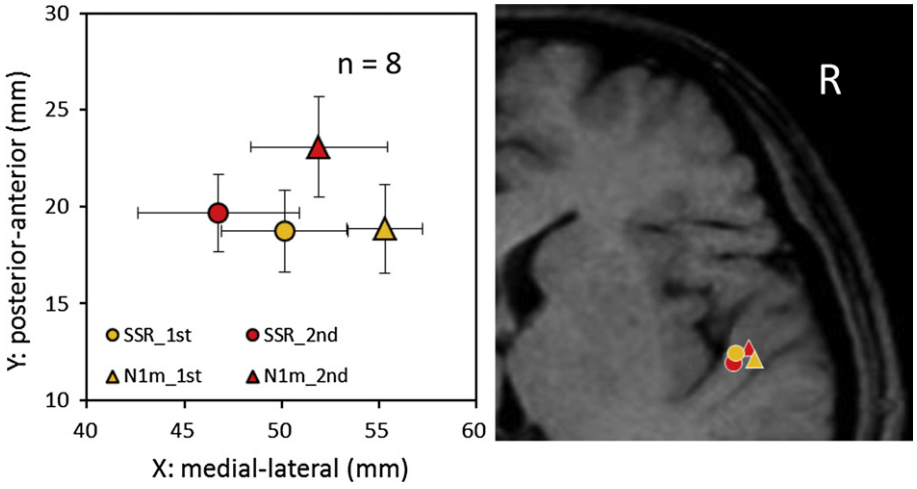

Fig. 6. Locations of single dipole sources of ASSR and N1m peak. Left side: grand mean locations across eight subjects for the first-tone and second-tone stimuli in Exp. I are shown in the *X*–*Y* coordinates, where bars indicate SE of the mean. Right side: source locations of one subject are superposed on his axial MR image.

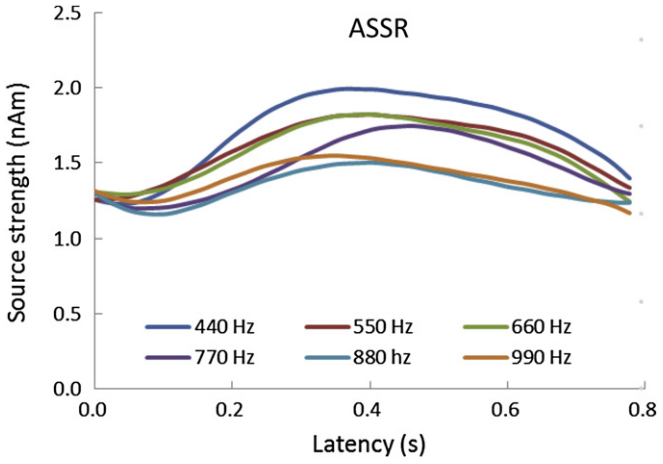

Fig. 7. Waveforms of the grand-mean source strength (dipole moment) of ASSR across ten subjects for different carrier frequencies of AM tones. The carrier frequencies are differentiated with colors, as shown under the waveforms.

anterolateral Heschl's gyrus across the area of the AI. The posterior activity has strong adaptation to the repetition of sound, subserving detection of novel sound in the "where" pathway of the auditory stream, while the anterior activity shows weak adaptation, subserving analysis of sound features in the "what" pathway. Consistent with this notion, it has been reported that the sources of the two subcomponents of N1m response, elicited by a tone burst in the right hemisphere, are localized in such a way that the late component is 4 mm anterior to the early component (Reite et al., 2009). In the present study, the second-tone N1m source was anterior (about 4 mm) to the first-tone N1m source. Given the two N1m activities having different adaptation patterns, we speculate that the posterior activity was strongly attenuated in the second-tone response by the preceding first tone, while the anterior weak-adaptation activity survived, and that the resulting gravity center of the N1m activity shifted to an anterior site. On the other hand, the anteriority of the second-tone ASSR source to the first-tone ASSR source was small (about 1 mm) compared to that of the N1m sources, though the statistical difference of the anterior–posterior separations between N1m and ASSR sources was not significant ($p = 0.061$). The small anterior shift of ASSR is in line with the notion that the multiple source adaptation mechanism,

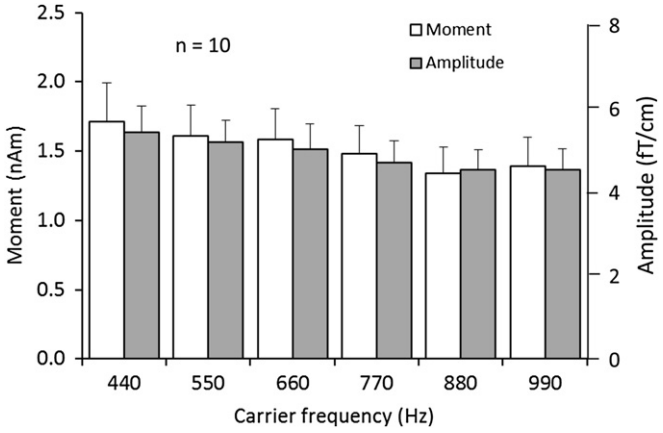

Fig. 8. Comparison of the dipole moment and the amplitude of ASSR (shown in Fig. 5). Grand-mean values across ten subjects are shown for different carrier frequencies. Bars indicate SE of the mean.

like that in N1m, does not exist in the ASSR activity that is located in the primary auditory cortex.

The amplitude of ASSR did not depend on the f_c of AM tones between 440 and 990 Hz having equal-loudness sound pressures (Exp. I). In the subsequent experiment (Exp. II) in which the sound level was changed in the same frequency range, the amplitude of ASSR, and the moment as well varied with the carrier frequency. Assuming the invariance of the amplitude of ASSR with carrier frequency at equal loudness found in Exp. I, the observed high correlation with SPL suggests that the amplitude of ASSR was proportional to the sound level in this frequency range. To make a quantitative comparison of the carrier frequency dependence of the amplitude/dipole moment of ASSR, we describe here some results of previous studies in which long continuous sounds of more than 200 s were used as the stimulus. Pantev et al. (1996) used Gaussian tone pulses of 60 dB nHL (normal hearing level) in a wide frequency range of 250 Hz to 4 kHz. Although not stated explicitly in their paper, the sound pressure of 60 dB nHL may have a variation of SPL of about 5 dB decrease from 500 to 1000 Hz. Their results indicated that the magnitude of ASSR has a weak decrease in about 10% of amplitude and a decrease of slightly less than 10% of moment in this low frequency range. The decrease of amplitude and moment becomes steeper at higher frequencies above 1 kHz. Wienbruch et al. (2006) used AM tones of 60 dB SL (sensation level) in a frequency range of 380 Hz to 6.6 kHz. From the sound detection threshold reported, we estimate the sound pressures to be about 12 dB higher at 500 Hz than at 1000 Hz. The observed decrease of the dipole moment in normal subjects was about 15% from 500 to 1000 Hz in the low frequency range. Ross et al. (2000, 2003) combined the results of their two separate studies of ASSR using AM tones of 70 dB SL in a wide frequency range of 250–4 kHz. From a regression line of those data on the frequency dependence of the moment, a slope of about 20% decrease is obtained for a low frequency range from 500 to 1000 Hz. This variation is slightly larger than the slope in the above studies but may be plausible if we consider that high SL values, i.e., sound pressures above the sensation level, have elevated SPL above the equal loudness curve at low frequencies. Thus, the high SL values they used, which correspond to 80 dB SPL described by Ross et al. (2003), may have augmented the ASSR response as the frequency was decreased in the low frequency range. Compared with these results, the observed decrease in the amplitude/moment of ASSR in Exp. II was about 15% from 500 to 1000 Hz, while the SPL of AM tones was reduced by 10 dB from 73 to 63 dB SPL. This reduction of the ASSR amplitude/moment is consistent with the observations in the previous studies. It is thus suggested that the results for the carrier frequency dependence of the amplitude/dipole moment of ASSR reported previously support the notion that the SPL of AM tones affects the magnitude of ASSR in an approximately proportional manner within the low frequency range of about 440–1000 Hz. The present study has also shown that a short AM tone with a period of 0.78 s in a consecutive train is sufficient to produce an observable change in ASSR.

Considering an approach with ASSR to the elucidation of "scale illusion" (Deutsch, 1974, 1975), separate stimulus tones in the right and left ears may be replaced by short AM tones having distinct modulation frequencies in the two ears. Then, the responses to the right and left stimuli generated in the auditory cortex are selected by the difference in the modulation frequency. In this process, smooth amplitude versus carrier frequency relation of the ASSR (such as that in Fig. 5, upper) is desirable. Such a single-valued relation would provide information on the temporal change of neural activities responding to the right- and left-ears' stimuli from the observed amplitude of ASSR. The method of frequency-tagged ASSR of MEG to differentiate the responses to the right- and

left-ear inputs was applied in the study on binaural interaction using long continuous AM tones (Fujiki et al., 2002; Kaneko et al., 2003).

The nonsignificant effect of carrier frequency on the ASSR observed in the low frequency range does not exclude conceivable effects at high frequencies exceeding 1 kHz. Animal studies on phase locking of the discharge of auditory nerves to sinusoidal tones have shown that the synchronization index, i.e., coherency of the phase locking, is a low-pass function with respect to the tone frequency, the corner frequency being about 600 Hz in guinea pigs (Palmer and Russell, 1986) and 1 kHz in cats (Johnson, 1980). For AM tones of a sinusoidal wave, the highest modulation frequency, to which phase locking to the envelope of AM waves occurs, is a function of the carrier frequency and about 0.8 octaves lower than the highest phase locking frequency to pure tones (Joris and Yin, 1992). The capability of phase locking to AM sounds in the auditory nuclei decreases from the auditory nerve, the medial geniculate body of the thalamus, to the primary auditory cortex AI along the auditory pathway (Schreiner and Urbas, 1988; Preuss and Müller-Preuss, 1990; Krishna and Semple, 2000). It has also been shown in the AI of the cat that higher synchronization occurs from AM, FM to click sounds having shorter rise times of the wave (Eggermont, 2002). This result indicates certain effects of the temporal structure of the carrier wave on the phase locking to AM sounds. Taken together, it is inferred that at high carrier frequencies exceeding 1 kHz, the phase locking to AM tones becomes less effective, resulting in a low-pass characteristic of ASSR above 1 kHz. Such frequency characteristics of ASSR were observed in some previous studies (Pantev et al., 1996; Wienbruch et al., 2006). To the other end of low carrier frequencies much lower than 500 Hz, e.g., around 200 Hz, only a small numbers of carrier waves exist within a cycle of 40 Hz-modulation period. In such a case, fine structures of the carrier wave, i.e., individual peaks, may determine the synchronization and the magnitude of ASSR.

Acknowledgments

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