A whole head MEG study of the amplitude-modulation-following response: phase coherence, group delay and dipole source analysis

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Abstract

Objective: The amplitude-modulation-following response (AMFR) is the frequency component detectable in the electroencephalogram (EEG) or magnetoencephalography (MEG) corresponding to the modulation frequency of an amplitude modulated tone used as a continuous acoustic stimulus. Various properties of the AMFR depend on modulation frequency, suggesting that different generators along the auditory pathway are involved. The present study addresses these issues on the basis of a whole head MEG experiment.

Methods: AM tones with modulators in the 40 Hz and 80 Hz range were presented unilaterally to 10 normal hearing subjects. Biomagnetic responses were recorded with a 151 channel MEG system. The data analysis concentrated on the phase coherence of the responses, group delays and the estimated location of underlying equivalent dipole sources.

Results: MEG AMFR is more reliably detected in the 40 Hz than in the 80 Hz range. Both response amplitude and phase coherence indicate clear bilateral activation over the parietal/temporal region. Dipole source analysis confirms that sources are located in or near the auditory cortex. Group delays at 80 Hz are shorter than at 40 Hz.

Conclusions: In both modulation frequency ranges MEG responses are dominated by activity in the auditory cortex, in apparent contrast with EEG data in the literature, pointing to dominant contributions of thalamic sources to the 80 Hz AMFR.

Keywords: Auditory evoked responses; Steady-state evoked responses; MEG; Phase coherence; Auditory cortex

1. Introduction

When the ear is continuously stimulated with a pure tone in the audible range, amplitude modulated with a frequency typically between 10 and 100 Hz, a distinct frequency component corresponding to the modulator (and its first few harmonics) can be detected in the EEG (Rickards and Clark, 1982, 1984; Rodriguez et al., 1986; Kuwada et al., 1986; Rees et al., 1986; Picton et al., 1987a). This response is known as the auditory steady-state evoked potential (Cohen et al., 1991) or, the term we will adopt, the amplitude-modulation-following response, AMFR (Aoyagi et al., 1993a,b,c). Since the modulation frequency itself is not present in the spectrum of the acoustic stimulus, its presence in the EEG is due to a nonlinear processing stage between the acoustic input to the ear and the generation of the EEG; an important nonlinearity responsible for extracting modulator information is formed by the rectifying transduction properties of the inner hair cells in the cochlea (Pickles, 1988). The interest for studying this type of evoked response goes back on the one hand to early work on the 40 Hz frequency following response (FFR), where a 40 Hz EEG component is recorded to repetitive stimulation with clicks or brief tone bursts (Galambos et al., 1981), and on the other hand to research on response properties to AM tones of single cells at various stages of the auditory pathway (reviewed by Eggermont, 2001). The interest in the AMFR has recently increased due to its clinical application for the objective, frequency specific assessment of hearing thresholds in infants: presence or absence of the modulation frequency response in the EEG at a particular stimulus level has proven a reliable indicator of peripheral hearing loss at the carrier frequency (Aoyagi et al., 1993c, Rance et al., 1995, 1998). Several detection methods of this type of
evoked potential have been developed, based either on an amplitude criterion of the generated spectral component or on phase coherence, i.e. on the fact that the response is phase-locked to the envelope of the stimulus (Aoyagi et al., 1993a; Picton et al., 1987b, 2001; Stapells et al., 1987).

The response properties of the AMFR have been shown to vary substantially over the range of modulation frequencies. In the early studies on the 40 Hz FFR it has been noted that clear responses can be obtained in awake, adult subjects, but not so during sleep (Jerger et al., 1986; Cohen et al., 1991). Studies on using the AMFR for objective audiometry in (sleeping) infants have universally shown that responses in the 40 Hz range are inconsistent (e.g. Stapells et al., 1988), but that reliable responses can be detected for modulation frequencies in the 80–100 Hz range (Aoyagi et al., 1993b; Rance et al., 1995; Lins et al., 1995); in that frequency range the response can also be obtained in awake adults, but with much lower amplitudes than at 40 Hz (Aoyagi et al., 1993b; Lins et al., 1995). The question whether this difference is primarily a matter of sleep vs wake condition, and/or if maturational effects are involved, does not seem to have been answered unequivocally. Then, there are differences in apparent latency, or group delay, of the response at different modulation frequencies. Group delay—or apparent latency—is a latency measure that is derived from the change of response phase with frequency; it is used as an indirect method of estimating neural response latency under steady-state stimulus conditions, where latency determination as commonly obtained from a transient response is obviously not feasible (Regan, 1989). Two distinctly different ranges of group delay in the 30–100 Hz range have been identified in EEG recordings, one around 40–50 Hz with delays in the order of 33 ms and one around 80–100 Hz with delays of about 15 ms (Kuwada et al., 1986; Cohen et al., 1991; John and Picton, 2000). Kuwada et al. (1986) mentioned two additional ranges for even lower or higher modulation frequencies. In magnetoencephalography (MEG) studies, Romani et al. (1982) reported clearly larger group delays in the order of 49 ms for a 32 Hz modulator, and varying with ipsilateral vs contralateral stimulation. Hari et al. (1989) report group delays of about 54 ms in the 40 Hz range, also clearly larger than earlier EEG results (Picton et al., 1987a; Stapells et al., 1984). Ross et al. (2000) distinguished three ranges of group delays at 20, 40 and 80 Hz, with group delays in both 40 and 80 Hz ranges again distinctly larger than the aforementioned values from EEG studies.

The sensitivity of the response to the vigilance of the subject, the possible involvement of maturational factors and the differences in group delay have raised the question of which are the dominant neural generators of the response. In the present paper we describe results of a study in which we have addressed the above and related questions using MEG. MEG has been applied to auditory steady-state responses in several earlier studies (e.g. Romani et al., 1982; Mäkelä and Hari, 1987; Hari et al., 1989; Pantev et al., 1996; Ross et al., 2000), which addressed e.g. the detectability of the response, the variation of amplitude with modulation frequency, group delays and particularly the location of equivalent dipole sources, the latter so far mainly at 40 Hz repetition or modulation rates. These studies were based on recording with a limited number of MEG channels covering at most one unilateral parieto-temporal area. In the present study we have used a 151-channel whole-cortex MEG system, which allows detailed comparison of simultaneously recorded ipsilateral vs contralateral responses (cf. Pantev et al., 1998) and of group delays and dipole source analysis based thereupon. To allow for comparison with some essential EEG results in the literature 4 EEG channels were co-recorded. Additionally, we present an analysis of phase coherence in the MEG response, which has thus far only been applied to EEG studies of the AMFR (for review see Picton et al., 2001). Based on this approach, a systematic comparison of two different modulator ranges ~40 and ~80 Hz is elaborated. An essential part of this study concerns the analysis of equivalent dipole sources underlying the MEG responses at different modulation rates. In particular, comparisons of e.g. response strength and group delays between left and right hemisphere and between different modulator ranges are also elaborated at dipole source level.
recording, both for off-line synchronization of the responses with the stimulus. After D/A conversion the stimulus signals were amplified using a commercial hi-fi audio amplifier. Stimuli were presented to the subject’s left ear, while the right ear was masked with broad band noise. Tubal insert phones (EarTone 3A) were used with 110 cm plastic tubes and foam eartips. Stimulus level was 70 dB nHL as calibrated using a sound level meter (Bruel and Kjaer 2230) with a DB0138 2 cm³ coupler. Stimuli with different modulation frequencies were presented in random order.

MEG recordings were made with a 151-channel whole-cortex MEG system (CTF Systems Inc., Vancouver, Canada). The sensors are uniformly distributed on the helmet surface with mean spacing of 3.1 cm. The SQUID sensors are first-order axial hardware gradiometers with 2 cm coil diameter and 5 cm base line. In addition there is an array of 36 reference sensors (12 magnetometers and 24 gradiometers) that were used for ambient noise cancellation (both in experiment and in model computations) by means of software formation of third-order synthetic gradiometers (Vrba et al., 1998). The total system noise level is less than 0.13 fT/√Hz. Head movement was restricted with foam pads inserted between head and helmet; localization coils at the nasion and left and right pre-auricular points were used to determine the head position at the beginning and end of each acquisition and were also used to define the head coordinate system (+ x = anterior, + y = left, + z = superior). Simultaneously with the MEG recordings, EEG responses were recorded from 4 Ag–AgCl electrodes located at Fpz, Cz, T7 and T8 with a reference on the left (ipsilateral) mastoid. MEG/EEG data were recorded continuously for 250 s at a sample rate of 625 Hz (40 Hz modulator range) or 1250 Hz (80 Hz modulator range) and stored for off-line analysis. An anti-aliasing filter at 1/3 of the sample frequency was used. At the end of the experiment, head shape was recorded using another localization coil placed at about 100 consecutive locations over the scalp. Recordings were made in a magnetically shielded room (Vacuumschmelze GmbH, Germany). Subjects were sitting in a reclining chair and were asked to keep their eyes open during the investigation. To assure the wake condition of the subjects, the investigator communicated with them using an intercom system between each 4 min data acquisition block, and permanently monitored them with a video camera.

To allow more detailed analysis of the estimated dipole source locations, MR scans were obtained in two subjects. Three-dimensional high-resolution T1-weighted images were obtained using a 1.5 T Siemens Magnetom Vision MRI system.

2.3. Data analysis

2.3.1. Averaging and filtering

First, occasional MEG channels with excessive noise level and occasional (mostly occipital) channels with strong MCG were identified and discarded from further analysis. The first part of the subsequent data analysis largely parallels the approach by Aoyagi et al. (1993a). The 250 s data from each experiment were split into 1000 segments of 250 ms duration, starting at the onset of each trigger signal, which were subsequently averaged in 10 subgroups of 100 segments. These unfiltered ‘group averages’ were used for the evaluation of phase coherence and group delays. In addition to the 10 group averages, the grand average was also determined. The actual response to the acoustic stimulus is characterized by discrete spectral components at the modulation frequency and its harmonics. Even after the aforementioned signal averaging, however, these components have a signal-to-noise ratio unfavourably low for e.g. dipole source analysis. Therefore, and because contributions from higher harmonics are very small (cf. Galambos et al., 1981), the averaging procedure was repeated after filtering the 250 s of raw data with a narrow band-pass filter around the modulator. A phase invariant band-pass filter with an amplitude transfer characteristic with a cosine-square profile and 3 dB points at 1 Hz above and below the modulation frequency was applied; thus, also a base line offset was removed. The filtered grand average data were used to generate response maps and for further analysis steps based on the amplitude of the response, especially the dipole source analysis.

2.3.2. Phase coherence

A steady-state response is characterized by its amplitude and phase spectra. The presence or absence of a response can not only be determined by an amplitude or signal-to-noise ratio criterion, but also by a detection criterion which looks for non-random phase behaviour: a response is considered reliable if its phase remains constant over time and/or is locked to the phase of the stimulus, rather than varies randomly. We have applied the analysis of phase coherence described by Fridman et al. (1984), using the statistical theory of directional data (Mardia, 1972), and as implemented for the AMFR by Aoyagi et al. (1993a). The method is based on the variance of phase of the spectral component among group sub-averages. The degree of reproducibility of phase among n sub-averages for Fourier component m is assessed by the so-called component synchrony measure (CSM; Aoyagi et al., 1993a)

\[
CSM(m) = \left[ \frac{1}{n} \sum_{i=1}^{n} \cos \varphi_i(m) \right]^2 + \left[ \frac{1}{n} \sum_{i=1}^{n} \sin \varphi_i(m) \right]^2
\]

This quantity permits a statistical decision to be made as whether the recorded waveform represents stimulus-locked activity or uncorrelated background activity from the brain. CSM varies between 0 and 1. When the phase \( \varphi_i(m) \) is the same for all sub-waveforms, CSM equals 1, indicating the mth Fourier component to be perfectly phase-locked with the stimulus. When the phase changes randomly (corresponding to non-correlated background activity and noise), the CSM approaches 0 with mean and standard deviation
(SD) equal to 1/n and \((n-1)/n^2\), respectively (Fridman et al., 1984). A CSM value (at the frequency of the modulator) close to 1 is therefore likely to reflect an auditory evoked response. Following the procedure of Aoyagi et al. (1993a), a response can be considered present if the CSM value is greater than 0.385 (mean + 3SD); this criterion coincides approximately with a 95% confidence limit as we verified using a Monte Carlo simulation. For the reliable measurement of signal phase used to calculate group delays in the present study a stricter criterion of CSM > 0.575 (mean + 5SD) was used.

2.3.3. Group delay

Unlike the case of a transient evoked response, the latency of a steady-state response cannot simply be measured in the time domain. For a steady-state response the delay elapsed between stimulation of the ear and the occurrence of the response can be determined in an indirect way from the slope of the phase–frequency curve, which in a system where this delay is independent of frequency, is linear. Thus, the apparent latency is defined as

\[
\tau = \frac{1}{2\pi} \frac{d\varphi}{df_{\text{mod}}}
\]

(cf. Kuwada et al., 1986; Regan, 1989; Cohen et al., 1991; Ross et al., 2000), a quantity also known as group delay in physical wave theory (e.g. Lighthill, 1978). Under the aforementioned condition this quantity is identical to the conventional travel time (or phase delay) that we are after. In the present data the group delay \(\tau\) was determined by measuring the phase difference between response and stimulus envelope at each modulation frequency, and fitting a regression line to the phase–frequency data in the 40 and 80 Hz modulation frequency range, respectively, after unwrapping the phase with respect to 2\(\pi\) discontinuities. Data points that did not meet the criterion for significant phase coherence were excluded from this analysis. All results were corrected for the acoustic delay caused by the tube connecting the speaker with the ear insert.

2.3.4. Dipole source analysis

Dipole source analysis was performed based on a least-squares fit to the filtered grand average magnetic responses of data simulated with a spherically symmetric head model, to that end a sphere was fitted to the individual subject’s head shape, and the location of its centre related to the localization of headcoils. All results in this study are based on a fit with a stationary dipole model, i.e. a dipole with a location fixed in time, but strength and orientation varying freely over time (Scherf and von Cramon, 1985; de Munck et al., 2002). Three different source configurations were evaluated for each dataset: (A) one single dipole, (B) two fully independent dipoles, and (C) two dipoles with left–right symmetric location but independent time functions for orientation and strength (also named the semi-symmetric model). A parameter optimization procedure was applied starting from the best fitting location obtained with a 500-point global search.

3. Results

Illustrative examples of magnetic field maps are shown in Fig. 1, for modulation frequencies of 40 and 80 Hz, respectively. Fig. 1 represents grand average responses, band-filtered at the modulation frequency, and shows map at 8 different time samples, covering one cycle of the modulator. The responses show that there is clear bilateral activation, characterized by two bipolar patterns over the parieto-temporal regions, with response amplitudes in the RT range. Both at 40 and 80 Hz modulators responses are larger over the right (contralateral) than over the left (ipsilateral) hemisphere; comparison of Fig. 1a and b also indicates that the response amplitude is smaller for the 80 Hz modulator than for the 40 Hz modulator. Both Fig. 1a and b demonstrate how the response pattern varies periodically with the cycle of the modulator, including a polarity reversal of the bipolar pattern. The 40 Hz data shown in Fig. 1a were representative for all 40–56 Hz modulators in all 10 subjects albeit that occasionally the response over the left hemisphere was weaker than shown in Fig. 1a. Clear response patterns in the 80–96 Hz range as shown in Fig. 1b were found in 6 out of 10 subjects, though generally the responses were much weaker over the left than over the right hemisphere. In the remaining 4 subjects the responses in this frequency range had a low signal-to-noise ratio to the extent that no distinct bipolar patterns could be visually recognized in the response maps.

Phase coherence was evaluated for each MEG channel separately by calculating from the unfiltered sub-averages the CSM, for all Fourier components (Eq. (1)). Maps of the CSM at the modulation frequency are presented in Fig. 2a and b, for the same 40 and 80 Hz datasets for which amplitude maps were shown in Fig. 1a and b, respectively. Fig. 2 demonstrates that for both modulators there is a high phase coherence in MEG channels covering extended parietal and temporal areas, both over the left and right hemispheres. As was the case for response amplitude, this figure suggests that CSM values are larger (and extend over a larger area) over the right than over the left hemisphere, and are larger at 40 Hz than at 80 Hz. The CSM results plotted in Fig. 2 are representative for all 40–56 Hz modulator data in all subjects, and for the 6 subjects producing clear responses in the 80–96 Hz modulator range. The remaining 4 subjects, with no recognizable bipolar amplitude patterns in that frequency range, generally had weak or absent CSM maps. Fig. 3 demonstrates, by plotting grand average results over 10 subjects and over the 5 best right hemispheric channels, how phase coherence varies across the different Fourier components (Eq. (1)). The curves plotted for each 40 Hz range modulator indicate that phase coherence shows a greatly significant peak at
Fig. 1. Projected magnetic field maps of the AMFR to a 70 dB, 1000 Hz tone modulated with a 95% modulation depth, for 8 different time instants during the cycle of the modulator, as indicated below each plot for (a) modulator 40 Hz, subject DE and (b) 80 Hz, subject MP. Note the different amplitude scales in (a) and (b).

Fig. 2. Projected maps of the CSM, evaluated at the modulation frequency, for a 70 dB, 1000 Hz tone modulated (a) at 40 Hz and (b) at 80 Hz, for the same datasets as in Fig. 1.
the modulation frequency, but is about the level of 0.1 for random phase behaviour (namely, \(1/n\) with \(n = 10\)) for adjacent frequencies. In some subjects small scalp areas with (weakly) significant phase coherence were also found at the second harmonic frequency of a 40 Hz range modulator. In other subjects such phase coherence was absent, reason why the peaks at the second harmonic in the curves plotted in Fig. 3 do not exceed the 0.385 significance level. Results for the 80 Hz modulator range were similar to those depicted in Fig. 3, with generally lower peak CSM values, and a smaller amount of phase coherence at the second harmonic. Similar conclusions hold for left hemisphere, 40 Hz range data and stronger so for left hemisphere, 80 Hz range data.

To evaluate the variation of MEG response amplitude with modulation frequency, the 5 MEG channels with the largest root-mean-square (rms) response amplitude were identified, and their average rms amplitude determined, for each subject and each modulation frequency, both on the left and on the right hemispheres. The results pooled over the 10 subjects as presented in Fig. 4a, indicate that on average response amplitudes are maximal around a modulation frequency of about 44 Hz with a systematic decrease towards 56 Hz, and are smaller by a factor of 2–3 in the 80–96 Hz range. Responses in the ipsilateral, left hemisphere are, on average, 30–40% lower than in the contralateral, right hemisphere. The amplitude differences between the 40 and 80 Hz range are statistically significant, and so are the differences between left and right hemispheres (two-tailed (paired) \(t\) test, \(p << 0.01\)). To evaluate the variation of the CSM (at the modulator) as a function of modulation frequency a similar analysis of CSM was pursued. For each subject, modulation frequency and hemisphere, the 5 MEG channels with largest CSM were identified and their average determined. Results pooled over subjects are presented in Fig. 4b. The right hemisphere, 40 Hz range data correspond to the peak CSM values in Fig. 3. The general pattern is comparable to that observed for response amplitude in Fig. 4a, however, the relative reduction in the 80 Hz vs the 40 Hz range is smaller for the CSM than for response amplitude. Differences between 40 and 80 Hz range and between left and right hemispheres are again highly significant (two-tailed (paired) \(t\) test, \(p << 0.01\)). Similar trends as in Fig. 4 were obtained when not the maximal amplitude and...
CSM values were evaluated but rather their overall average or median, or e.g. the number of channels with significant CSM.

As is not further shown, EEG amplitudes and CSM are smaller at 80 Hz than at 40 Hz; clear responses could generally be obtained at Cz and Fpz electrodes, but at 80 Hz EEG channels T7 and T8 showed small amplitudes and CSM often not different from background noise.

For the analysis of group delays, the following procedure was applied in each subject. For both 40 and 80 Hz modulator ranges, 5 MEG channels with largest amplitudes were identified both in the temporal and in the parietal response areas of both hemispheres (cf. Fig. 1). Regression lines were computed from the combined phase–frequency data for each set of 5 channels, to produce MEG group delays for left and right temporal and parietal response areas. Also, group delays were determined for EEG channels Cz and Fpz. Finally, the results for the different subjects were pooled, leading to means and standard deviations as summarized in Table 1. Statistical tests indicated that MEG group delays do not significantly differ between left and right hemispheres, but that there is a weakly significant difference between parietal and temporal regions, both left and right in the 40 Hz modulator range (two-tailed paired t test, 0.01 < p < 0.05) but not in the 80 Hz range (right hemisphere testable only). Comparing right hemispheric MEG with EEG group delays, MEG delays are significantly larger than EEG delays when different channels are considered together (MEG parietal and temporal; EEG Cz and Fpz; unpaired t test, p << 0.01). The same is found when comparing parietal or temporal MEG group delays with EEG Cz at 40 and 80 Hz and with EEG Fpz at 40 Hz (paired t test, p < 0.05); this same comparison, however, applied to parietal or temporal MEG channels with EEG FPz at 80 Hz revealed only a weak significance (0.05 < p < 0.1).

Dipole source analysis was restricted to the 6 subjects which, except for the commonly observed clear responses in the 40 Hz modulator range, also produced clear responses in the 80 Hz modulator range, at least over the right hemisphere. For the majority of these datasets consistent results were found between the 3 models applied (one single dipole, a pair of semi-symmetric dipoles and two fully independent dipoles) in the sense that: (1) the solution for the single dipole fit was in the right hemisphere where the responses had appeared largest; (2) the fits for the dipole in the right hemisphere across the 3 approaches were within about 1 cm from one another; and (3) the estimated dipole locations in the left hemisphere with the two independent dipole models were close to that obtained from the semi-symmetric model, and in accordance with the maps (cf. Fig. 1). The dipole results presented below are those based on the two independent dipole model but include only the data where the aforementioned 3 consistency criteria were met. In particular, some datasets allowed no reliable dipole estimates in the left hemisphere for 80 Hz range modulators, consistent with absence both of bipolar patterns in the maps and of a significant CSM. These left hemispheric results are therefore also not further considered. Fig. 5 shows a projection of the estimated dipole sources in the MRI scan of one of the subjects. The main observation here is that both 40 and 80 Hz range dipole sources are located in or near the auditory cortex, in or near the posterior part of

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<td>EEG sensors</td>
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<td>Fpz</td>
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<tr>
<td>Right dipole</td>
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Table 1

Group delay (in ms) in the 40 Hz and 80 Hz modulator ranges, for MEG responses, EEG responses, and MEG source time functions (mean ± SD across N ≥ 6 subjects)

Fig. 5. Estimated dipole locations plotted in an MRI scan of subject CB. Five dipole locations associated with the modulation frequencies in the 40 Hz range (circles), and 5 dipole locations for modulation frequencies in the 80 Hz range (triangles) are shown as projections through the MR slices.
the Sylvian fissure, with approximately left–right symmetrical location. Projection of computed dipole source locations in the second subject for which an MRI scan was available gave a very similar result. Notably, the 80 Hz range dipoles have very similar locations to 40 Hz range dipoles. While statistically comparing the 5 dipole locations in the lower with those in the higher modulator range, no statistical differences were found in either x, y or z direction in the nasion–ear coordinate system in the vast majority of comparisons that could be made. As a next step the 5 dipole locations in each hemisphere of each subject and in each modulator range were averaged to a ‘centre of mass’ location. Table 2 presents the result as analyzed over subjects. The difference in location between 40 and 80 Hz modulator ranges is typically less than 0.3–0.5 cm. There was no systematic trend as to the relative location of the two centre of mass sources. Since a between-subject comparison is potentially confused by differences in head shapes of the subjects, the dipole locations as found in each subject’s spherical head model were also mapped into a unitary sphere and then analyzed; again no significant differences in location were found, neither between modulator ranges, nor between subjects. Comparisons were also made regarding left–right symmetry of the dipole locations; no systematic differences were found across the group, though some within-subject comparisons revealed significant differences in location in any of the 3 directions.

Finally, an analysis was made of the source time functions of the estimated dipoles. Their rms amplitudes were determined, and the results plotted in Fig. 4c to allow for a 40–80 Hz and for a left–right comparison at source level. The variation of source strength is qualitatively similar to that in MEG signals in Fig. 4a; statistical comparison between 40 and 80 Hz modulator range, and between left and right, reveal similar significance levels.

Also, the phases of the source time functions were used to determine group delays at the source level; the results, included in Table 1, indicate that these group delays are highly similar to those determined on the basis of the MEG signals as such.

### 4. Discussion

In this study we have concentrated on properties of the amplitude modulation following response for modulators between 40 and 100 Hz, although this type of response can in principle be detected over a much wider frequency range, from several Hz to several hundreds Hz (Rickards and Clark, 1982, 1984; Rees et al., 1986; Kuwada et al., 1986; Rodriguez et al., 1986). When analyzing an EEG or MEG steady-state response, and particularly when considering its neural origins, one should be aware that all stages of the auditory pathway are in fact simultaneously active; depending on the location of the auditory nuclei, the orientation of the current sources therein and their response properties to AM tones, contributions from some sources will dominate those from others in the response measured at the scalp. It is a general property of the auditory system that neural responses phase-lock to the envelope of an amplitude modulated tone, up to a certain cut-off frequency above which phase-lock breaks down; this cut-off frequency however, becomes low gradually towards higher stages along the auditory pathway (e.g. Eggermont, 2001). Thus it is expected a priori that the AMFR to more high-frequency modulators will contain relatively more contributions from earlier stages along the auditory pathway as compared to more low-frequency modulators. Obviously, such contributions will therefore demonstrate shorter latencies, and also smaller attention effects.

We chose 40–56 and 80–96 Hz modulators because from an earlier preliminary exploration, and from most of the relevant literature, AMFR amplitude was found to be larger than at other (e.g. intermediate) frequencies, and because we were particularly interested in the properties of the 80–96 Hz AMFR in view of its highly relevant clinical application of objective hearing threshold assessment e.g. in infants. Detection of the electric AMFR in that context is commonly based on a signal-to-noise criterion, a phase coherence criterion, or a combination thereof (for a review see the study by Picton et al., 2001). Generally, inclusion of some phase coherence criterion increases the detection sensitivity, since the signal-to-noise ratio is low even at clear supra-threshold stimulation levels. The same was observed in our MEG data: the response has low amplitudes in the FT range (Figs. 1 and 3a) and could not easily be distinguished from the background noise. Instead, phase coherence is a suitable criterion for the detection of a response in the background noise. When interpreting the CSM maps in Fig. 2 one should be aware that a larger extent of areas with significant CSM most likely reflects stronger sources and a better signal-to-noise ratio, and not
necessarily a larger spatial extension of the source. The results in Fig. 2 show that significant phase coherence is found over large areas of the scalp, coinciding with the regions where the amplitude maps reveal a clear bipolar pattern. The fact that phase coherence is less reduced than response amplitude in comparing the 80 vs 40 Hz range (Fig. 3) indicates that phase coherence is a particularly robust detection criterion in the 80 Hz modulator range. Only for some of the 40 Hz range datasets significant phase coherence was also observed at the second harmonic of the modulator. The bilateral activation upon monaural stimulation (Fig. 1) goes back to the various crossing and non-crossing pathways, particularly at the level of the auditory nuclei in the brainstem. The observation that both amplitudes and CSM are larger over the contralateral than over the ipsilateral hemisphere (Fig. 4) corresponds to the asymmetry in amplitudes of the source time functions, in combination with the equally deep location of dipole sources in left and right hemispheres. The asymmetry in source strength is consistent with e.g. the observation at single cell level, both in the higher brainstem and thalamic nuclei and in the cortex, that contralateral stimulation often produces more excitation than ipsilateral stimulation, which may sometimes even be inhibitory (e.g. Irvine, 1992; Clarey et al., 1992), and also with other MEG studies of auditory evoked responses (Pantev et al., 1998).

Elaboration of AMFR group delays by various authors suggests that several different modulator ranges can be distinguished, ~20, ~30–70, ~80–110 and >150 Hz, each with a different group delay (Kuwada et al., 1986; Cohen et al., 1991; Ross et al., 2000). The group delays we find in our 40 Hz range MEG data (Table 1) are notably shorter than the 49 ms reported in the MEG study by Romani et al. (1982), the 54 ms reported by Hari et al. (1989), and the 48 ms of Ross et al. (2000); for the 80 Hz range our data are very similar to the 26 ms reported by the latter authors. Our data do not replicate the left–right asymmetry in group delay for unilateral stimulation reported by Romani et al. (1982). The potentially significant difference in group delay observed between our temporal and parietal MEG channels, at ~40 Hz but not at ~80 Hz, is puzzling and may point to the presence of more than one cortical source with slightly different location; indeed, several of our data when analyzed with a moving dipole model indicated source locations moving back and forth in time, which may be consistent with two or more sources alternatively being dominant (cf. Hari et al., 1989; Pantev et al., 1996; Gutschalk et al., 1999). The finding that group delays determined for MEG sensor channels and for dipole source time functions are similar (Table 1) was not unexpected given that the data in each hemisphere were effectively described by a single dipole. Our EEG group delays are quite comparable to delays given by e.g. Kuwada et al. (1986) (31 ms at 40 Hz) and Cohen et al. (1991) (34 and 14 ms at 40 and 80 Hz, respectively), and those estimated in a less formal way by e.g. John and Picton (2000) (17 ms at 80 Hz). The discrepancy between MEG and EEG group delays in the present study is therefore consistent with findings in the literature on MEG or EEG, respectively. However, the general conclusion that MEG group delays are different from EEG group delays has to be made with some care, since there is also a significant difference between EEG group delays for Fpz and Cz channels and between temporal and parietal MEG channels, and because most but not all comparisons between specific EEG and MEG channels revealed a strongly significant difference in group delay (Table 1). A more solid approach would be to base such a comparison on source time functions as derived from (simultaneous) full MEG and full EEG mapping in the same subjects, but the latter were not available in our study.

Latency measures have been an important factor in discussion of the sources involved in the AMFR. The 40 Hz AMFR/FFR has often been viewed as a repeated Pa/Na complex (e.g. Hari et al., 1989; Plourde et al., 1991; Pantev et al., 1993; Ross et al., 2002; cf. Eggermont and Ponton, 2002) because the group delay of this steady-state component is comparable to the latency of that MLR component. Since the Pa/Na complex is presumably generated in the auditory cortex (Scherg and von Cramon, 1986; Pellizone et al., 1987; Yvert et al., 2001; Borgmann et al., 2001) the same origin is generally assumed for the 40 Hz steady-state response. However, considering the AMFR/FFR as a repeated Pa/Na complex is questionable since the latter is based on typical MLR stimulus rates of 2–5 Hz, and the expected change in Pa/Na waveform for rates of 40 Hz due to increased habituation/adaptation is largely denied. Also, the latency vs group delay comparison is problematic since it depends strongly on the waveform of the Pa/Na complex as demonstrated in an illustrative simulation study by Hari et al. (1989). Background of the difficulty in making such comparisons obviously is that the physical concept of group delay, namely to describe the travel time of wave packages (Lighthill, 1978), can hardly be expected to cover the transient brain response to e.g. click stimuli. In the present context, the slope of the phase–frequency relation was analyzed primarily as an indirect way to estimate the phase delay—the conventional travel time—in a steady-state stimulation condition. The necessary assumptions for that approach (Regan, 1989) seem largely fulfilled, namely (1) frequency-invariance of the delay within the 40–56 and 80–96 modulation frequency ranges as considered and (2) the absence of significant filter effects along the dimension of the modulation frequency (Fig. 4).

Based on dipole source analysis Romani et al. (1982) and Mäkelä and Hari (1987) reported cortical origins of the 40 Hz MEG steady-state response. Pantev et al. (1995, 1996) made a comparison based on MEG between 40 Hz steady-state responses, auditory middle latency response peak Pa and long latency response peak N1. They concluded that all equivalent dipole sources are located in or near the auditory cortex. However, the medio-lateral tonotopic organization
of the 40 Hz response was similar to that of the N1 but opposite to that of the Pa. Given the mirror-image spatial orientation of tonotopic maps in different cortical fields (e.g. Rauschecker et al., 1995; Pantev et al., 1995) this would suggest that, at least when measured magnetically, both N1 and 40 Hz steady-state responses originate from secondary regions of the auditory cortex, while Pa is dominated by primary cortical activity. Dominant contributions from primary auditory cortex for 80 Hz MEG AMFR, as a potential conclusion from the present study, would fit within that framework. In contrast with this scheme however, Ross et al. (2002) reported systematic differences between MEG 40 Hz AMFR and N1 source locations; therefore the issue of how the dominant sources of the different responses are related does not seem to have been answered unequivocally.

The dominant sources of the 80–100 Hz EEG AMFR have not been identified with the same certainty. Most authors however, again based on considerations of latency compared to middle latency response components and sensitivity to arousal effects, consider higher brainstem or thalamic nuclei the most likely dominant generators (Kuwada et al., 1986; Cohen et al., 1991; Aoyagi et al., 1993a,b,c; John and Picton, 2000). Recently, Herdman et al. (2002) concluded from an EEG-based dipole source analysis of the AMFR for modulators of 12, 39 and 88 Hz that a brainstem source dominates the 88 Hz response, while the 39 Hz response also contains brainstem contributions but is dominated by cortical sources. Fitting the present MEG data with two cortical sources and additionally a thalamic source was found not to lead to improved fits compared to the model with bilateral cortical sources only, for either modulator range (not shown in further detail). Therefore, we conclude that contributions from thalamic sources to MEG AMFR are negligible, also for 80 Hz range modulators.

The dipole source analysis in the present report therefore unequivocally indicates that sources of the magnetically recorded AMFR are lying in the auditory cortex, both for modulators in the 40 Hz and in the 80 Hz range. There is substantial scatter and overlap across the estimated source locations for the two modulator ranges (Figs. 4 and 5) which can at least partly be explained by the uncertainty in the estimated inverse model solutions. No definite conclusion can be drawn from the present dipole source analysis as to whether the 40 and 80 Hz responses do or do not originate from two anatomically different cortical fields. Notably, the variation between solutions from single dipole, two semi-symmetric dipole and two free dipole models was mainly in the anterior–posterior and medial–lateral directions, but not in the inferior–superior direction, which is plausible since this variability presumably reflects spread of activation through the supratemporal plane which is nearly orthogonal to the longitudinal axis. The dipole source locations for the 40 Hz range are at least qualitatively similar to those reported by Romani et al. (1982) for a normalized spherical head model. The only study so far including a similar range of modulation frequencies in an MEG experiment (Ross et al., 2000) gives values for the mean estimated source location of $x = 1.29$ cm, $y = 4.30$ cm and $z = 6.12$ cm, without reporting systematic difference between different modulator ranges; these average values are in the same range as we found in the present study (Table 1), after accounting for the slight difference in definition of the origin of the coordinate system between Ross et al. (2000) and the present study.

In conclusion, the available data on MEG dipole source localization of Pa, N1 and AMFR (in different modulator ranges) unequivocally indicate that all responses are dominated by cortical sources. However, latencies and group delays of the various responses (and particularly the group delays of the AMFR source time functions), and the orientation of their tonotopic maps as reported in the literature, suggest that a distinction can be made between different stages of cortical processing, in the sense that the 80 Hz range AMFR and Pa originate from primary cortical regions, and 40 Hz AMFR and N1 from secondary auditory cortex. The present study once again illustrates that EEG and MEG responses may demonstrate notable differences in response characteristics. In particular, the apparent disparity between EEG and MEG group delays suggests that for the equivalent EEG responses a slightly different scheme may apply with—because of the shorter group delays—relatively stronger contributions to the AMFR from lower stage, more deeply located auditory brain areas. This hypothesis requires further testing, e.g. by combined full EEG and MEG mapping of the different responses and dipole source analysis based thereupon. In this paper we have adopted a primarily auditory view on the properties of the auditory steady-state responses. A perhaps even more important generation mechanism might be in a resonance of cortical cell populations, at their intrinsic gamma frequencies, as brought about by periodic sensory input in the 40 Hz range (cf. Ross et al., 2002). If this is a dominant part of the physiology behind the AMFR, the general view may of course become quite different, but many of the foregoing considerations on group delays and source localizations are expected to hold unalteredly.

References


