

Right Hemispheric Laterality of Human 40 Hz Auditory Steady-state Responses

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Hemispheric asymmetries during auditory sensory processing were examined using whole-head magnetoencephalographic recordings of auditory evoked responses to monaurally and binaurally presented amplitude-modulated sounds. Laterality indices were calculated for the transient onset responses (P1m and N1m), the transient gamma-band response, the sustained field (SF) and the 40 Hz auditory steady-state response (ASSR). All response components showed laterality toward the hemisphere contralateral to the stimulated ear. In addition, the SF and ASSR showed right hemispheric (RH) dominance. Thus, laterality of sustained response components (SF and ASSR) was distinct from that of transient responses. ASSR and SF are sensitive to stimulus periodicity. Consequently, ASSR and SF likely reflect periodic stimulus attributes and might be relevant for pitch processing based on temporal stimulus regularities. In summary, the results of the present studies demonstrate that asymmetric organization in the cerebral auditory cortex is already established on the level of sensory processing.

Keywords: amplitude modulation, auditory evoked magnetic fields, hemispheric asymmetry, magnetoencephalography, pitch processing

Introduction

Outstanding skills in audition allow humans to develop a wide range of communication capabilities, such as speech and music. Brain areas involved in audition include the auditory cortices located in the left and right temporal lobes. Specialization of both hemispheres for processing distinct features of sound is assumed as a basic principle for the evolution of human communication performance (Corballis, 1989). From studying functional asymmetry in the human auditory system we expect to gain new insights into the specialization of brain for processing the auditory environment.

The dichotomy of speech processing in the left hemisphere (LH) versus music processing in the right hemisphere (RH) was investigated intensively in lesion studies and by means of neuroimaging methods as reviewed, for example, by Tervaniemi and Hugdahl (2003). The question of which acoustical features are asymmetrically processed and result in hemispheric specialization for speech and music was posed in a positron emission tomography (PET) study by Zatorre and Belin (2001). Their subjects listened to tone sequences, which were complex in either temporal or spectral structure. The results showed LH specialization for rapid temporal processing and an RH specialization for spectral processing. This is consistent with laterality of speech versus music processing under the assumption that the analysis of spectral fine structure of sound is more dedicated to music perception (Zatorre *et al.*, 2002) and that processing of fast temporal changes is more important for speech percep-

tion (Phillips and Farmer, 1990; Tallal *et al.*, 1993). Evidence for laterality of pitch and melody processing in auditory cortices was gained from a functional magnetic resonance imaging (fMRI) study using melodies, irregular noise stimuli and regular sounds that have a perceived pitch quality (Patterson *et al.*, 2002). Asymmetry toward the right hemisphere was found when the stimulus contained melodic information, whereas noise and constant pitch stimuli showed symmetrical bilateral activation of primary and non-primary auditory cortices. Further evidence that the anatomical and functional organization of human speech perception is lateralized and organized in multiple pathways involving temporal, parietal and frontal cortices was provided by neuroanatomical studies of non-human primate auditory cortex and functional neuroimaging in humans (Scott and Johnsrude, 2003).

Beside those functional specializations in both hemispheres, anatomical structures of the central auditory system may cause response asymmetries. A prominent example is the often observed dominant activation in the hemisphere contralateral to the stimulated ear. The neurons of the ascending auditory pathway cross toward the hemisphere contralateral to the stimulated ear at the level of the brainstem (Evans, 1982). Thus, the auditory pathway consists of a combination of large number of crossing and less non-crossing fibers. Consequently, left and right auditory cortices respond to monaural stimuli asymmetrically. Asymmetrical activation has been already reported in several auditory evoked response (AER) studies. In electroencephalographic (EEG) recordings, Wolpaw and Penry (1977) found larger N1/P2 amplitudes contralateral than ipsilateral to the stimulated ear. With single channel magnetoencephalography (MEG), Reite *et al.* (1981) demonstrated larger N1m responses to click stimuli in the hemisphere contralateral to the stimulus (right +35%, left +45%) with a tendency for larger responses in the left hemisphere. This result was confirmed with 38% larger N1m amplitudes to contralateral tone-burst stimulation (Pantev *et al.*, 1986). Larger contralateral auditory evoked 40 Hz steady-state magnetic fields and sustained fields in the RH than in the LH were reported by Tiihonen *et al.* (1989) using trains of click stimuli. Both response components were even larger in the RH with binaural stimulation, which was not the case for the simultaneously recorded N1m amplitudes. These studies point out that auditory evoked responses are larger in the hemisphere contralateral to the stimulated ear.

Whole-head MEG studies allow simultaneous recording of activity from both hemispheres and corroborated earlier findings of dominant contralateral N1m responses, however, no significant amplitude differences between left and right hemispheres were found with alternating left and right ear pure-tone

stimulation (Makela *et al.*, 1993) or binaural stimulation (Pantev *et al.*, 1998). The observation of predominant contralateral activation was also made in an fMRI study that investigated passive listening to pulsed tonal stimuli (Scheffler *et al.*, 1998), and in a combined MEG/fMRI study about FM discrimination (Woldorff *et al.*, 1999). These studies were able to distinguish between activation of different areas of the auditory cortex utilizing the high spatial resolution of fMRI methods. An fMRI study by Devlin *et al.* (2003) reported, for the first time, a left hemispheric predominance in human primary auditory cortex for sound processing.

The focus of the present study was the neuronal activity generated in the human primary auditory cortex. We compared the magnitudes of auditory steady-state response (ASSR) to 40 Hz AM tones evoked in right and left primary auditory cortex in order to answer the question of a probable hemispheric dominance for the 40 Hz ASSR. The ASSR is an oscillatory activity, mainly originating from primary auditory cortex. It is phase locked to the rhythm of an auditory stimulus, typically sequences of clicks (Galambos *et al.*, 1981; Hari *et al.*, 1989) or amplitude modulated tones (Rees *et al.*, 1986; Picton *et al.*, 1987). Although the functional relevance of the ASSR is not fully understood, close relations to temporal processing in the auditory system are assumed because the ASSR follows the time-course of temporal fluctuation in the sound stimulus. Recent studies demonstrated that the temporal dynamics of the ASSR reflect both temporal integration (Ross *et al.*, 2002) and temporal resolution (Ross and Pantev, 2004) in auditory processing. Since the experimental design of the present study allowed not only for recording of 40 Hz ASSRs, but simultaneously for recording of transient, and sustained responses from the central part of the auditory system, these components have been compared with respect to their laterality. Further dissociation between the effects of the 'side of stimulation' and 'responding hemisphere' on response laterality in the human auditory system was made feasible from comparison of responses to monaural and binaural stimulation.

Materials and Methods

Retrospective analysis was carried out on MEG data recorded in three experiments using binaural and right and left ear monaural stimulation with 40 Hz amplitude-modulated sound.

Subjects

Thirteen subjects (seven females) participated in the experiment with binaural stimulation, and 11 (five females) and 12 (five females) in the experiments with right and left monaural stimulation, respectively. The subject groups for binaural and monaural experiments were exclusive; however, some subjects participated in the monaural experiments. The subjects were between the ages of 22 and 50 years (mean age 33 years), all were right-handed as verified with the Edinburgh handedness questionnaire (Oldfield, 1971). Hearing thresholds below 15 dBHL between 250 and 8000 Hz were ensured using pure-tone clinical audiometry. Informed consent was obtained from each subject after the nature of the study was fully explained. The experiments were part of a larger project entitled 'Magnetic Studies of Human Hearing', which had received approval from the Ethics Committee of the Baycrest Centre for Geriatric Care. The subjects were paid for their participation.

Auditory Stimulation

The auditory stimuli were 40 Hz sinusoidal amplitude modulated tonebursts of 500 Hz carrier frequency. The experiments were designed to answer different questions. Therefore, stimulus durations were different with 600 ms for monaural stimulation and 2.0 s for binaural stimulation. In the experiments with monaural stimulation the AM tones were

presented alternating with 180° phase shift in the modulation signal. This allowed separation of the transient gamma-band response and the ASSR because the latter was cancelled out in the sum of all responses but the evoked gamma-band response remained. Alternatively, in the difference between responses with 0 and 180° AM phase the transient response was cancelled out, but the ASSR was kept. The stimuli were presented with a stimulus onset asynchrony (SOA) uniformly randomized between 2.0 and 3.0 s for the two experiments with monaural stimulation and between 3.5 and 4.5 s for binaural stimulation. All experiments were divided into two recording sessions lasting less than 1 h. In the experiment with monaural stimulation this time was sufficient to perform eight blocks containing 256 stimuli. With the longer SOA used for binaural stimulation, 12 blocks of 128 stimuli could be recorded. Stimulus intensity was set to 60 dB above the individual sensation threshold. The stimuli were presented under control of STIM software (Neuroscan Inc., Sterling, VA) using Etymotic ER3A transducers, which were connected via 1.5 m plastic tubes to silicon earpieces fitting to the subject's ears.

Data Acquisition

The MEG recording were performed in a quiet magnetically shielded room using a 151-channel whole-head neuromagnetometer (VSM-Medtech, Port Coquitlam, BC, Canada). The detection coils of this MEG device are configured as axial first order gradiometers and are almost equally spaced on the helmet shaped surface. Detailed information about the general MEG method was given by Vrba and Robinson (2001). The magnetic field data were sampled at the rate of 312.5 s⁻¹ in the binaural experiment and at 625 s⁻¹ in the experiments with monaural stimulation after low-pass filtering at 100 or 200 Hz, respectively.

Subjects were seated comfortably in upright position. They were asked to remain alert and compliance was verified using video monitoring. In order to control for confounding changes in vigilance, subjects watched a self-selected soundless movie. Possible head movements were monitored using three detection coils attached to the subject's forehead and the earpieces. Subjects' heads did not move more than 8 mm during either recording block. Thus, all recorded data were accepted for data analysis.

Data Analysis

Stimulus-related epochs of the magnetic field data, including pre- and post-stimulus intervals of 250 ms, were averaged after rejecting artifact-contaminated epochs in which magnetic field changes larger than 2 pT occurred. For the analysis of the ASSR, consecutive overlapping epochs of 50 ms were repeatedly sampled and averaged every 25 ms beginning 200 ms after stimulus onset until stimulus offset in order to exclude the ASSR onset interval (Ross *et al.*, 2002). Source analyses, based on the model of spatio-temporal equivalent current dipoles (ECD) in a spherical volume conductor, were applied to the N1m component of the transient AER and to the ASSR. For each subject, two ECDs (one in each hemisphere), defined by their moment, orientation, and spatial coordinates, were used to model the N1m, the ASSR and the sustained field, respectively. Sample points of magnetic field data used to approximate the two ECDs were in a 30 ms interval centered around the N1m peak, a 5 ms interval centered around the maximum ASSR waveform, and the interval from 400 ms after stimulus onset to the stimulus offset for the sustained field. The dipoles in both hemispheres were fitted simultaneously to the 151-channel magnetic field distribution. First, we modeled the data with a mirror symmetric pair of dipoles. The resulting source coordinates were then used as starting points to fit the dipole in one hemisphere while the coordinates in the other hemisphere were kept fixed. We then switched between hemispheres and repeated the last step until the source coordinates showed no further change.

A source space projection method was used to collapse the 151 time-series of the MEG sensors into a single waveform of magnetic dipole moment, which is a measure of neural activation strength (Tesche *et al.*, 1995). The method is based on the linear relation between the dipole moment $q(R)$ at the location R of the cortical source and the measured field $b(r)$ at each sensor position r , given by $b(r) = L(r,R) \times q(R)$, in which the elements of the leadfield matrix $L(r,R)$ denote the sensitivity of each sensor at position r for the source at location R (Hamalainen

et al., 1993). The pseudo-inverse of the leadfield $L(r,R)$ is used to calculate a set of weighting factors performing the reverse mapping of the magnetic field into the dipole moment. The dipole moment waveform can be considered as the signal, measured with a virtual sensor, which responds maximally to the region of interest in the brain. Contributions from other regions and uncorrelated system noise are reduced or cancelled out. Three independent spatial filters were calculated for each subject using the estimated source coordinates and directions for the N1m, the ASSR and the SF. Dipole estimation and source space projection was performed with the CTF software package (VSM-Medtech, Port Coquitlam, BC, Canada).

P1m and N1m amplitudes and latencies were obtained from the peak in the intervals between 40 and 80 ms and 80 and 120 ms, respectively. The ASSR amplitude was obtained from least-square approximation of a 40 Hz sine wave to the source waveform in the interval between 250 ms and the stimulus offset. The amplitude of the transient gamma-band response was defined as an envelope peak in the 24–48 Hz filtered source waveform modeled using ECD coordinates of the ASSR. SF amplitude was defined as the mean of the source waveform in the interval between 400 ms after stimulus onset and stimulus offset.

Individual laterality indices (LI) were calculated for all response components (P1m, N1m, gamma-band, ASSR and SF) as the difference between right and left hemispheric responses normalized by the sum of responses,

$$LI = (R - L) / (R + L)$$

Thus, the LI was +1 for a response completely lateralized to the RH, zero for a symmetrical response, and -1 for a response completely lateralized to the LH.

Results

Individual Waveforms

Clearly identifiable auditory evoked responses were observed in every subject. MEG waveforms obtained from one individual with binaural stimulation and arranged in a flattened projection of the sensor positions above the head (Fig. 1) exhibit the transient P1m–N1m–P2m and SF responses in the 24 Hz low-pass filtered signals (top, left) and the oscillatory activity of the ASSR in the 24–48 Hz band-pass filtered signals (top, right). Iso-contour maps of the magnetic field strength at time points of the maximum of the N1m response and a maximum of the ASSR demonstrate typical field distribution caused by a pair of dipolar sources (Fig. 1, middle part). For the example shown in Figure 1, N1m, SF and ASSR amplitudes were larger in the RH than the LH (Fig. 1, bottom part).

Source Localizations

N1m, ASSR and SF source coordinates in both hemispheres were estimated for each subject from repeated-measurement data in the two monaural and the binaural stimulation experiments. Confidence intervals for the individual mean source coordinates were <8 mm. Paired *t*-test applied to the individual distances between N1m and ASSR source coordinates indicated that ASSR sources were located 8.2 mm more medially in the RH

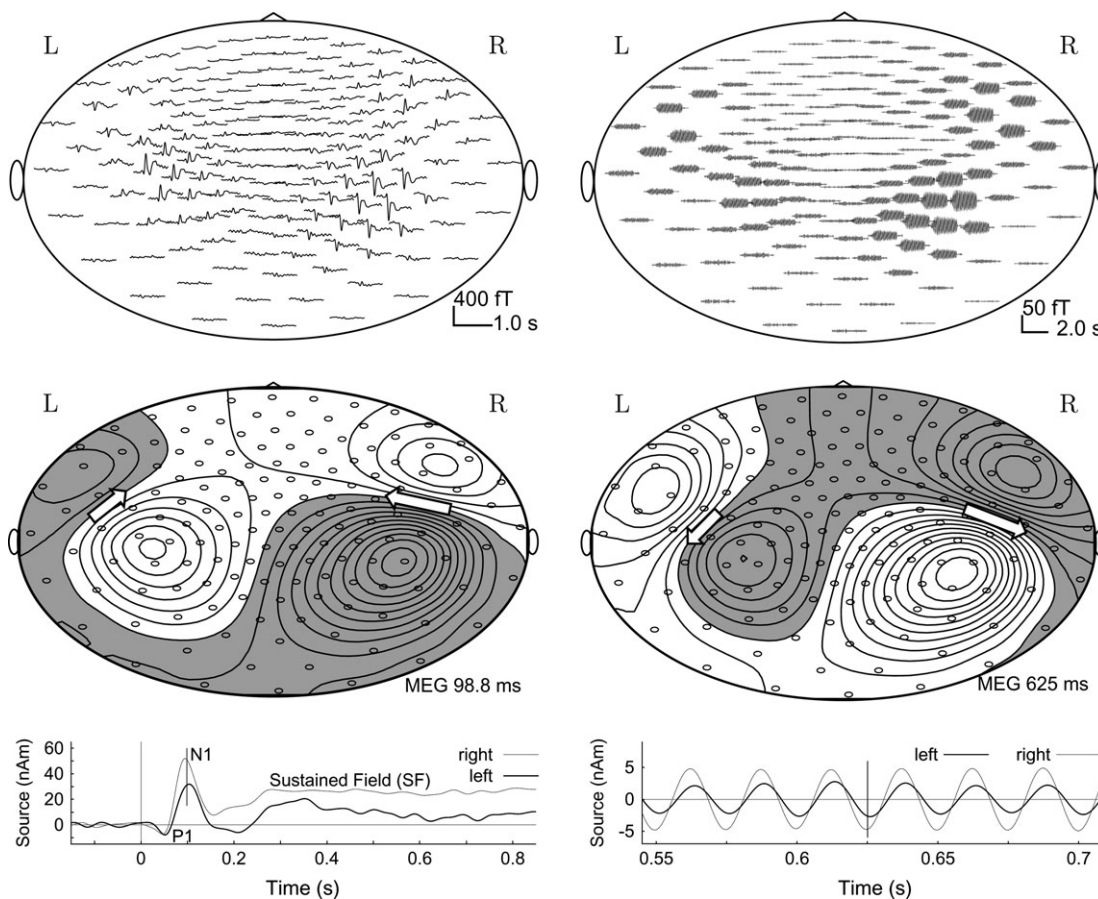


Figure 1. Individual time-series of the auditory evoked magnetic field obtained with binaural stimulation. In the top row, MEG waveforms are arranged in a flattened projection of the sensor positions. Left: 24 Hz low-pass filtered transient responses. Right: 24–48 Hz band-pass filtered steady-state responses (note the different scales). Iso-contour maps of the magnetic field at the time of response maxima showing dipolar pattern above both hemispheres are shown in center row. The arrows depict models of single equivalent dipoles in the left and right hemispheres. Time-series of the source strength for the transient responses (left) and the oscillating ASSR (right) are shown in the bottom row. The vertical lines denote the time point corresponding to the iso-contour maps above.

$t(34) = 9.59, P < 0.00001$] and 9.5 mm in the LH [$t(34) = 6.94, P < 0.00001$]. SF source locations were not significantly different from those of the N1m. N1m source locations were located, on average, 5.2 mm more anteriorly in the RH than in the LH [$t(34) = 3.38, P = 0.002$]. ASSR sources were also asymmetrically localized and were located on average 3.2 mm more anteriorly in the RH than in the LH ($t(34) = 3.03, P = 0.005$). Larger variance in location existed for the SF than N1m or ASSR sources. Thus, SF source locations were not found to be significantly different between hemispheres.

Source Waveforms

An overview of the grand averaged source waveforms in response to monaural and binaural stimulation is given with Figure 2. The waveforms for the ASSR, the low frequency components (P1m-N1m, SF), and the transient gamma-band response are separately displayed. The ASSR to left ear stimulation (Fig. 2*b*) had considerably larger amplitude in the contralateral RH than in the ipsilateral LH. In contrast, a smaller ASSR amplitude in the RH than in the LH was observed in general with right ear stimulation (Fig. 2*d*). However, ASSR amplitude was still larger in the RH than in the LH, regardless of stimulation side. For binaural stimulation, a consistently larger ASSR amplitude was observed in the RH than in the LH (Fig. 2*f*). SF amplitudes showed very similar behavior as the ASSR in relation to the sides of stimulation. With monaural left ear stimulation the SF amplitude was more than twice as large in the RH than in the LH, whereas an SF of almost equal size was elicited with monaural right ear stimulation. With binaural stimulation the SF was generally larger in the RH than in the LH. The N1m amplitudes were consistently larger in the hemisphere contralateral to the monaurally stimulated ear. However, the N1m to binaural stimulation were larger in the RH than the LH. Finally, the transient gamma-band responses

were larger in the contralateral hemisphere, when left (Fig. 2*a*) and right ear (Fig. 2*c*) stimulation was applied. With binaural stimulation (Fig. 2*e*) the transient gamma-band responses were larger in the RH than in the LH.

Laterality Indices

Hemispheric asymmetry of the auditory evoked responses (N1m, SF and ASSR) was quantitatively described with laterality indices, which are summarized in Figure 3. For right ear stimulation, the N1m response was lateralized to the left hemisphere; the mean laterality index was $LI = -0.17$ and the 95% confidence interval (95% CI) was -0.34 to -0.04 . Significantly larger N1m amplitudes in the right hemisphere were found for left ear stimulation ($LI = 0.23$, 95% CI = 0.05 – 0.40). No pronounced hemispheric dominance for the N1m was observed with binaural stimulation ($LI = 0.04$, 95% CI = -0.09 to 0.20). Likewise, the transient gamma-band response was significantly larger in the contralateral hemisphere regardless of the ear stimulated. P1m amplitudes were larger in the LH than in the RH for right ear stimulation, but were similar between hemispheres for left ear stimulation. Transient gamma-band and P1m responses did not show pronounced asymmetries when the stimuli were presented binaurally. In contrast to the transient responses, the ASSR did not completely follow the principle of contralateral hemispheric dominance. When the stimulus was presented monaurally to the right ear, ASSRs were not significantly lateralized ($LI = 0.02$, 95% CI = -0.10 to 0.18). ASSRs were lateralized to the RH for binaural stimulation ($LI = 0.24$, 95% CI = 0.12 – 0.37), and lateralized even more strongly to the RH for left ear stimulation ($LI = 0.44$, 95% CI = 0.29 – 0.65). SF amplitudes followed the same characteristic of symmetry for right ear stimulation and expressed progressively more laterality to the RH for binaural and left ear stimulation.

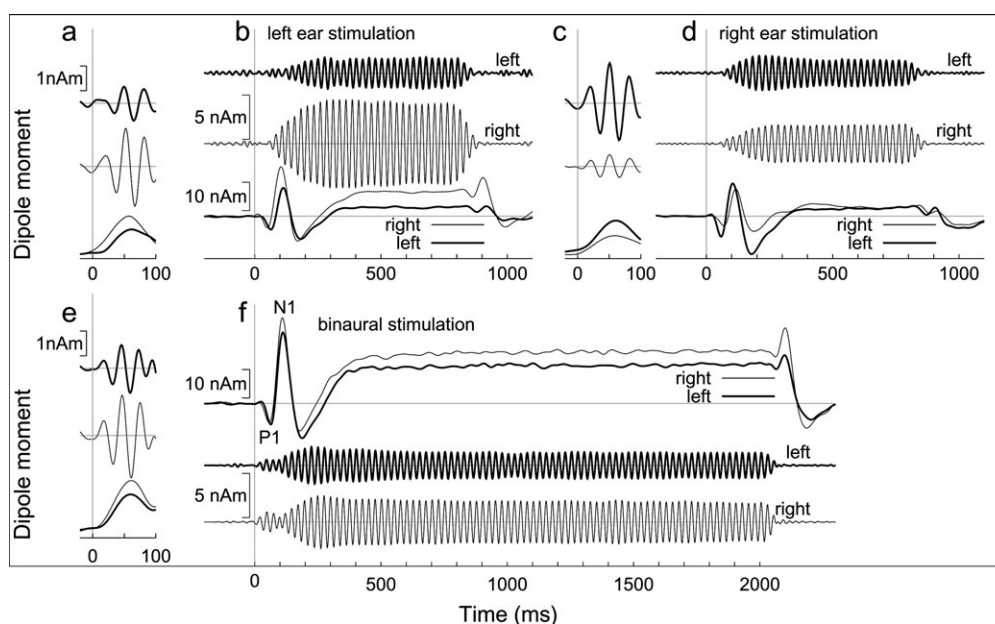


Figure 2. Dipole moment waveforms obtained from sources in the left (thick lines) and right (thin lines) hemisphere. (a) Individual 24–48 Hz band-pass filtered transient gamma-band responses (upper traces) and grand averaged gamma-band signal envelopes (lower trace) obtained with left ear stimulation. (b) Group averages of 24–48 Hz band-pass filtered ASSR (upper traces) and 24 Hz low-pass filtered N1-P1-P2-SF responses (lower trace) (c) Transient gamma-band responses and (d) ASSR and low-pass filtered transient responses obtained with right ear stimulation (e) and (f) Response waveforms to binaural stimulation.

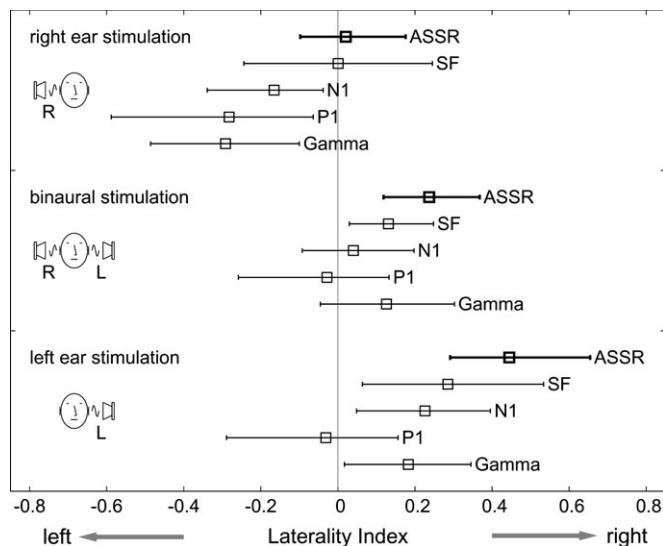


Figure 3. Group mean laterality indices (square symbols) for the transient gamma-band response, the P1m, N1m, SF and ASSR obtained with monaural left and right ear stimulation and binaural stimulation. The error bars denote the bootstrapped 95% CIs for the mean.

Effect of the Ear of Stimulation

LI for the N1m, SF and ASSR components were approximated by linear models $ax + b$, with the independent variable $x = \{-1, 0, 1\}$ denoting the side of stimulation (left, binaural, right). The slope a describes the effect of the side of stimulation on the LI and the intercept b an additional bias specific for the response component. The results of this regression analysis are summarized in Table 1. For all types of responses, significantly negative slopes a of the regression lines were found. This means that all response components were more lateralized to the hemisphere contralateral to the stimulated ear. The mean slope of -0.203 was not significantly different between the response components. The intercepts of the regression lines were significantly ($P < 0.05$) larger than zero for the ASSR ($b = 0.219$) and the SF ($b = 0.164$). Intercept for the N1m and the transient gamma-band response were not significant. A significantly negative intercept for the P1m occurred ($b = -0.112$). In addition to the common effect of the stimulated ear, significant bias toward the RH was found as a specific feature for the ASSR and the SF. N1m and gamma-band responses did not show a bias toward a particular hemisphere. The bias of P1m LI was negative; however, it was smaller than those for ASSR and SF. In addition to the effect of the stimulated ear, P1m was lateralized toward the LH.

Individual Variability of the LI

The individual laterality indices obtained with binaural stimulation are summarized in Figure 4 for the N1m, SF and ASSR. Bar graphs represent the mean LI of 12 repeated observations for each subject. All single LI measures are indicated by square symbols in the left panel and depict individual variability. Error bars in the right panel denote the 95% CI for the mean. Bar graphs in the left panel are aligned to each subject and allow within-subject comparison of LI for different response components. The same data are ordered by the LI value in the right panel and illustrate the distribution of LI for the N1m, SF and ASSR.

Table 1

Linear regression of laterality indices for the various evoked components

Component	Intercept	Slope	<i>t</i> -test (<i>n</i> = 34)	Adj. <i>r</i> ²	<i>F</i> (1,33)
ASSR	0.219	-0.235	$P < 0.001, t = 5.51$ $P < 0.001, t = 4.69$	0.382	22.0
SF	0.164	-0.175	$P = 0.008, t = 2.83$ $P = 0.023, t = 2.38$	0.121	5.7
N1	0.034	-0.176	NS, $t = 0.74$ $P = 0.002, t = 3.40$	0.237	11.6
P1	-0.112	-0.214	$P = 0.025, t = 2.35$ $P = 0.001, t = 3.59$	0.259	12.9
GAMMA	-0.032	-0.230	NS, $t = 0.73$ $P = 0.001, t = 3.68$	0.269	13.5

N1m responses were lateralized to the RH in five out of 13 subjects, lateralized to the LH in five subjects and balanced between hemispheres in three subjects. The median N1m LI was not significantly different from zero. SF was lateralized to the RH in six out of 13 subjects, lateralized to the LH in two subjects and balanced between hemispheres in five subjects. The subject with the median SF LI showed an RH asymmetry. However, this did not reach significance. The LI for ASSR showed significant RH asymmetry in 11 subjects and LH asymmetry in two subjects. The median LI was >0.2 , indicating significant RH dominance. The two subjects with left ASSR laterality also had larger N1m and SF responses in the LH than the RH (subject 9) or did not show a significant asymmetry for the N1m and SF responses (subject 6). Conversely, the subject with largest RH laterality of the ASSR (subject 8) also has the largest RH laterality for the N1m and SF response.

The interaction between the LI for the ASSR, SF, and N1m responses becomes more obvious from the scatter-plot of the LI for ASSR and SF versus LI of the N1m (Fig. 5). The regression analysis revealed a significant effect of the LI of N1m on both the LI of the SF [$F(1,12) = 14.9, P = 0.003$] and the LI of the ASSR [$F(1,12) = 5.0, P = 0.048$]. Thus, subjects with a certain hemispheric dominance for the N1m response also had a dominant ASSR and SF in the same hemisphere. However, the inter-subject variability for the LI decreased systematically between N1m, SF and ASSR, indicated by decreasing slope of the regression lines for N1m, SF and ASSR in Figure 5. Additionally, the intercepts of regression lines for SF and ASSR were significantly larger than zero, denoting a shift of 0.13 toward the RH for the SF ($P = 0.01$) and of 0.20 toward the RH for the ASSR ($P = 0.002$).

Response Latencies

The N1m latency was consistently shorter in the contralateral hemisphere in the case of monaural stimulation. Mean N1m latencies for right ear stimulation were 13 ms longer in the RH (109 ms) than the LH (96 ms) [$t(11) = 3.42, P < 0.006$]. Mean latencies for left ear stimulation were 11 ms longer in the LH (102 ms) than in the RH (91 ms) [$t(9) = 4.41, P < 0.002$]. For binaural stimulation, mean N1m latencies of 101 ms in the RH and 103 ms in the LH were not significantly different. Latency asymmetries were smaller for the ASSR than the N1m response. For monaural right ear stimulation, the ASSRs in the LH were delayed by 2.5 ms compared with the ASSRs in the RH ($t(11) = 3.64, P < 0.004$). For monaural left ear stimulation, the ASSRs in the LH were 3.1 ms longer than in the RH ($t(9) = 2.85, P < 0.02$). For binaural stimulation, the mean ASSR latency was 0.4 ms shorter in the RH than in the LH; however, this difference was not significantly different from zero.

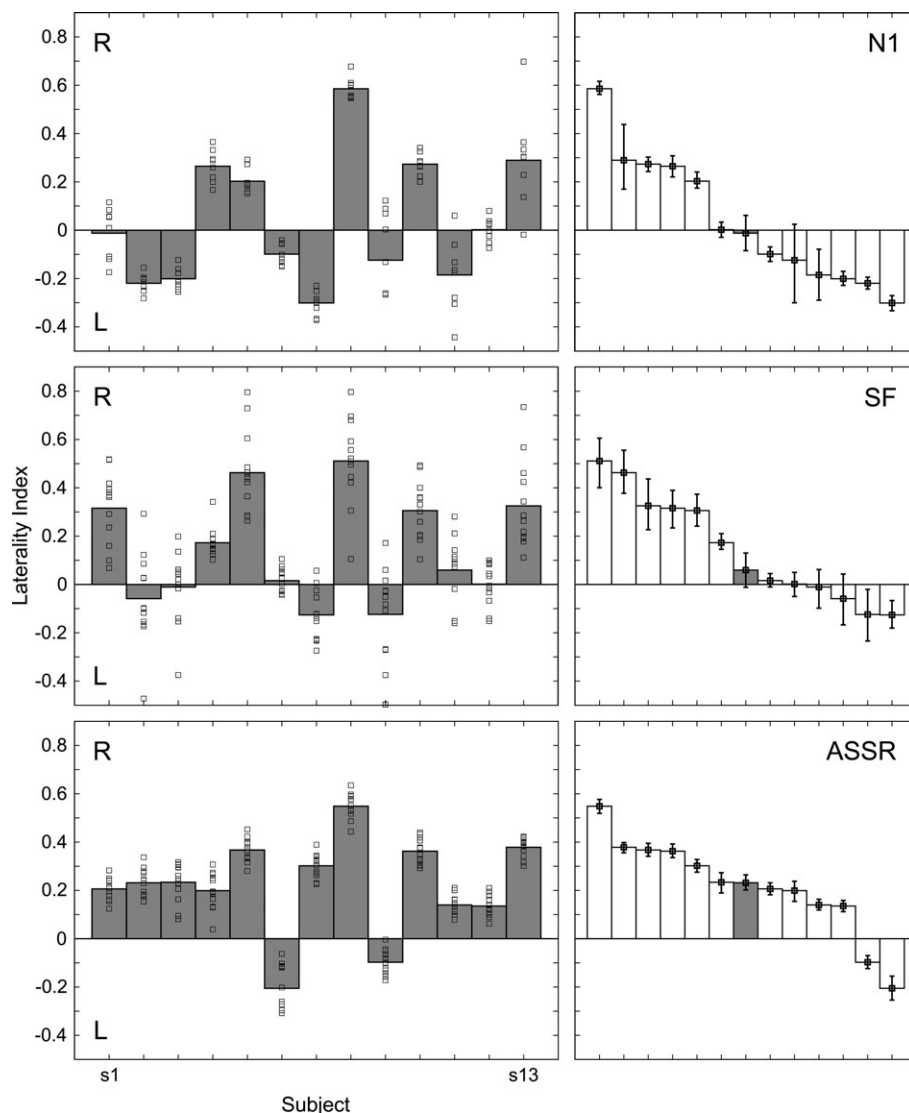


Figure 4. Individual laterality indices for the N1m, SF and ASSR for the case of binaural stimulation. The square symbols in the left diagrams denote the results of repeated measures and the filled gray bars the corresponding mean laterality index. The ordered diagrams on the right panel depict the distribution of laterality indices across the group. The error bars denote the 95% CIs for the individual mean values. The group median is represented by the filled gray bar.

Discussion

Studying hemispheric asymmetry of auditory evoked responses to monaurally and binaurally presented amplitude-modulated sounds revealed two main effects. First, all investigated transient AEF components (N1m, P1m and transient gamma-band response) and sustained components (ASSR and SF) showed similar dependencies on the side of stimulation. Changing the monaural stimulus from one ear to the other resulted in increased laterality toward the contralateral hemisphere. Second, in addition to the effect of the stimulated ear, the ASSR and SF showed a significant right hemispheric dominance. Despite several evidences for larger ASSR and SF responses in the RH, the RH dominance of the ASSR and SF has not been reported explicitly before. In this aspect, we shall discuss our MEG results in conjunction with previous MEG studies about laterality of the N1m response and fMRI and PET studies about hemispheric asymmetry in audition.

Although our study focuses on the ASSR, it compares ASSR laterality with those of simultaneously recorded transient and

sustained responses. Unfortunately, some overlap in time may occur between AEF components, and hence a completely independent measure of amplitudes would not be valid. One might assume that enhanced N1m amplitudes, as shown in Figure 2, might be caused by superimposition of an enhanced SF on a constant N1m. However, an onset latency of 150 ms for the sustained field was found by Picton *et al.* (1978). Therefore, we can assume that N1m and SF do not substantially overlap. This, however, could not be assumed for the off-responses and the P2m component of the AEF, which peaks at ~200 ms. Consequently, discussion of laterality of the P2m and off-responses would not be appropriate and it was excluded from this discussion.

ASSR Sources

Localization of cerebral sources of evoked responses was not a main goal of this study; however, source localization was performed as a prerequisite for source space projection of the magnetic field waveforms. Individual magnetic resonance

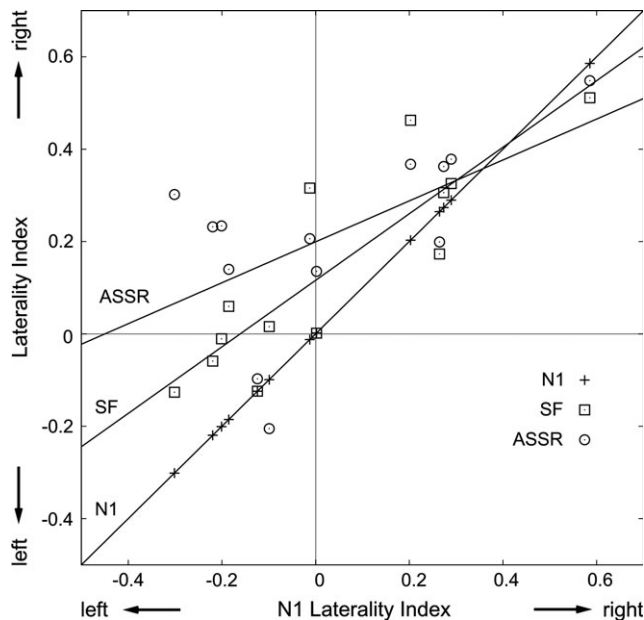


Figure 5. Individual laterality indices for the SF and ASSR obtained with binaural stimulation in relation to the LI for the N1m response and corresponding regression lines.

images were not available in all cases, which would allow assigning the obtained source coordinates to anatomical structures. The clear separation between more medial ASSR sources and more lateral N1m sources was taken as evidence for ASSR sources in primary and N1m sources in non-primary auditory cortex. Successful dissociation of the closely spaced cortical sources of N1m and ASSR is, however, consistent with previous results from simultaneous recordings of both response types (Pantev *et al.*, 1996; Engelen *et al.*, 2000; Ross *et al.*, 2002; Herdman *et al.*, 2003).

Source Location Asymmetries

Our result showing that ASSR sources were ~3 mm more anterior in the RH than in the LH is consistent with ASSRs located 6 mm farther anterior in the RH than in the LH (Teale *et al.*, 2003). Unfortunately, in their study amplitude data were not reported and thus it was not shown whether altered asymmetry in source location was accompanied by changes in functional asymmetry. The consistency of the RH anterior asymmetry of the ASSR, located on the medial part of the HG, with the same type of asymmetry of the N1m sources, located in more lateral parts of the HG and the supratemporal plane (Pantev *et al.*, 1996; Engelen *et al.*, 2000; Ross *et al.*, 2002; Herdman *et al.*, 2003), points to a general anatomical asymmetry (Rademacher *et al.*, 2001) between the right and the left hemispheres.

Inter-individual Variability

For each stimulus type, LI showed a wide range of variability between subjects. Thus, the lack of N1m laterality for binaural stimulation is mainly a group effect, whereas most individuals showed N1m lateralization toward left or right hemisphere. Using data from different subject groups prevented any intra-individual pairwise comparison of laterality indices. That the effects of contralaterality of the response and RH dominance for

the ASSR was significant regardless of the non-vanishing inter-subject variability indicates the robustness of the observations.

Ear Advantage

Lateralization toward the hemisphere contralateral to the stimulated ear was observed for all evoked response components. Approximately 40% larger N1m amplitudes in the contralateral hemisphere were found in previous MEG studies (Reite *et al.*, 1981; Pantev *et al.*, 1989). This corresponds to $LI = 0.166$ [$LI = (140 - 100)/(140 + 100)$] and is consistent with $LI = 0.176$ obtained for the N1m in the present study. If one hemisphere is specialized for certain auditory function, the principle of a dominant crossing pathway results in functional advantage for the ear contralateral to this hemisphere. For instance, the listener recalls the syllables better for right than left ear stimulation, when listening to dichotic presentation of concurrent consonant-vowel syllables (Hugdahl and Wester, 1992). This is accepted as a behavioural measure of left hemispheric specialization for speech processing (Tervaniemi and Hugdahl, 2003). The observation in our study that the effect of the stimulation side on laterality was almost the same for all response types, even if they originate from primary (e.g. ASSR) and non-primary auditory areas (e.g. N1m) is in line with the general dominant representation of auditory periphery in the contralateral hemisphere. Additionally, an asymmetry toward the RH for the ASSR is superimposed onto the general principle of contralaterality. P1m, N1m, SF and ASSR components are larger in the hemisphere contralateral to ear of stimulation, but an additional RH asymmetry does exist for the ASSR. Since the ASSR is a response to the (40 Hz) periodic structure of the stimulus, it can be assumed that the RH asymmetry indicates an RH specialization for processing the temporal periodicity of the sound.

A left ear advantage for detection of 40 Hz amplitude modulated sound was recently reported by Brancucci and San Martini (1999, 2003). They compared detection performances for slow amplitude fluctuation (1 Hz), perceived as loudness variation, and rapid amplitude modulations (6.67 Hz and 40 Hz), perceived as timbre quality of the sound. Although the left ear advantage was smaller for rapid than for slow amplitude fluctuations, processing of temporal sound structure was assumed for both rhythms. The result of left ear advantage for AM detection is consistent with the RH laterality of the 40 Hz ASSR found in our study. This supports the hypothesis that ASSRs are related to the auditory processing of temporal sound structures.

Sustained Response

The larger sustained responses to trains of periodic clicks than to irregular clicks as found in a MEG study by Gutschalk *et al.* (2002) was discussed as evidence for the SF as an indicator of pitch processing. This observation points to a possible functional relationship between SF and ASSR. The finding of common RH laterality for SF and ASSR in the present study gives further evidence for functional connections between SF and ASSR. Furthermore, the possible relation to pitch processing is in line with larger SF and ASSR amplitudes in the RH, which is widely accepted as being specialized for pitch processing.

Transient Gamma-band Response

The transient gamma-band response was lateralized toward the hemisphere contralateral to the monaurally stimulated ear. The

observed tendency toward RH laterality with binaural stimulation was not significant. Furthermore, a probable bias caused by imperfect separation of ASSR and transient gamma-band response cannot be excluded. Thus, in contrast to the ASSR, the evoked gamma-band response did not show a hemispheric preference. This result is in line with previous observations (Ross *et al.*, 2002) giving evidence that ASSR and transient gamma-band responses are distinct response components despite the fact that both are oscillatory responses at similar frequencies.

Interhemispheric Connections

Significantly longer latencies of the ipsi- than contralateral N1m response to monaural stimulation like those found in this study were reported previously (Elberling *et al.*, 1981; Pantev *et al.*, 1986, 1998; Rogers *et al.*, 1990; Makela *et al.*, 1993; Nakasato *et al.*, 1995). The complex bilateral structure of the ascending auditory pathways (Pollak *et al.*, 2003) prevents a straightforward explanation of faster transmission in the contralateral pathway. One explanation was suggested by Jancke *et al.* (2002), who assumed that crossing pathways have greater number of fibers and faster transmission speed than ipsilateral connections. Therefore, information presented monaurally to one ear could be transferred faster and with a higher efficiency to the contralateral auditory cortex. This asymmetry in information transfer could cause an asymmetry in information processing within the auditory cortices. Oe *et al.* (2002) observed in patients with fronto-temporal lobe infarction prolonged latency of the N1m response to ipsilateral stimulation in the intact hemisphere, whereas the latency of N1m to contralateral stimulation was not affected. Those results gave insights into inter-hemispheric connections suggesting that because of crossing fibers in the auditory pathway the contralateral cortex is activated first. Ipsilateral activation is then mediated through inter-hemispheric connections, presumably via the corpus callosum. Inter-hemispheric time delay of 6–10 ms was estimated in healthy subjects (Innocenti, 1986; Nowicka *et al.*, 1996). Early inter-hemispheric communication was also demonstrated by Ackermann *et al.* (2001), who found that the M50 (corresponding to the P1m response in our study) had two peaks: the first peak was larger in the contralateral than in the ipsilateral hemisphere and the second peak was larger in the ipsilateral than in the contralateral hemisphere. Identical latency between hemispheres for the M50 peaks is evidence against the hypothesis of different transmission delays in the left and right ascending auditory pathways. These findings indicate that initial contralateral processing followed by ipsilateral processing after a delay by inter-hemispheric transmission is a general principle in auditory pathways and might explain why the predominance of contralateral responses was seen in all AEF components in our study.

In contrast to N1m latency asymmetry of ~12 ms, the largest latency difference between ASSR in both hemispheres was <3 ms. This is less than half the ~6–10 ms trans-callosal transmission time and thus may conflict with an explanation of incorporating inter-hemispheric transmission delay. Also, the fact that the latency for oscillatory activity is ambiguous by multiples of one period of oscillation does not explain the observed small latency differences. However, oscillatory activity like the ASSR should not be discussed in terms of peak latencies only, but also in terms of the dynamics of the oscillatory network. Related simulation studies showed that synchronous oscillations in

neural networks could be established if transmission delays do not exceed about one-third of the period of oscillation. Thus oscillations in the gamma-band below 60 Hz are suggested to play an important role in inter-hemispheric synchronization (Engel *et al.*, 1991; Singer, 1993). We interpret the small phase differences between the ASSRs in both hemispheres as examples for highly synchronized activity. The tendency to an earlier ASSR in the right hemisphere under monaural stimulation was small and cannot be interpreted without support from further experimental data.

Comparison with MEG Studies

A substantially larger ASSR in the RH than in the LH to AM sounds at modulation frequencies between 40 and 56 Hz and 80 and 96 Hz were reported from a whole-head MEG study using left ear stimulation (Schoonhoven *et al.*, 2003). This result is in line with our observation that the ASSR laterality is largest with monaural left ear stimulation. In agreement with our result for RH dominance of the 40 Hz ASSR to binaural stimulation, larger ASSRs in the RH than in the LH were found at the fundamental frequency of binaurally presented periodic stimuli between 22 and 111 Hz (Hertrich *et al.*, 2004).

Schneider *et al.* (2002) deconvoluted the ASSR to binaurally presented AM tones and found, in agreement with our results, 20% larger ASSR amplitudes in the RH than in the LH. This corresponds to an LI of 0.09, which is smaller than the mean LI of 0.20 found in the present study. A possible explanation of the smaller effect may be the shorter duration of the stimulus bursts and the applied method of deconvolution, which does not incorporate the temporal dynamics of ASSR.

Comparison with PET/fMRI Studies

Hemispheric asymmetries in audition were investigated mostly using PET or fMRI methods (Zatorre and Belin, 2001; Devlin *et al.*, 2003). Comparing the results of those studies with the results of the present MEG study throws up several difficulties. Many of the fMRI and PET studies investigated higher cognitive functions in order to differentiate between the processing of speech and of music. The findings of those studies cannot be simply transferred to basic sound processing because different brain regions may be involved. Furthermore, the temporal dynamic of PET and fMRI signals is on a time-scale of seconds, and thus much slower than the time-course of MEG responses. Consequently, the correspondence between PET or fMRI activations and the various components of evoked responses in the MEG signal are widely unknown.

Devlin *et al.* (2003) investigated the functional asymmetry of sound processing in human primary auditory cortex (PAC) by means of fMRI. Their monaurally presented 5 Hz AM sounds had a much slower rhythm than the 40 Hz AM sounds used in the present MEG study. A clear left hemispheric advantage of PAC activation was observed regardless of the stimulated ear. However, the LI was larger with right ear stimulation. Thus, the blood oxygen level-dependent (BOLD) signal showed asymmetry toward the contralateral hemisphere, which is in line with our MEG results for all components of the AEF. The additional LH advantage, however, is in contrast to the larger ASSR and SF in the RH as observed with MEG.

Seifritz *et al.* (2002) dissociated between transient and sustained components of the BOLD signal and found the sustained activation to be more pronounced in the primary auditory cortex whereas the transient response was more

pronounced in the surrounding non-primary areas. The observed spatial separation between transient and sustained components in the fMRI suggests that the transient part of the fMRI signal might be related with the transient AEF (e.g. N1m) and the sustained parts of the fMRI signal may correspond to sustained components in the AEF (e.g. ASSR, SF). In another fMRI study Harms and Melcher (2002) disentangled transient and sustained components of the BOLD signal. For noise-impulse stimuli at a rate of 35 Hz, which is close to the 40 Hz modulation frequency used in our study, they found sustained and transient fMRI responses in medial and lateral parts of Heschl's gyrus, respectively. The similar dissociation in our MEG study between the ASSR in medial, and the transient N1m response in lateral, parts of Heschl's gyrus is striking; however, it is not sufficient to conclude a correspondence between the components of the AEF and fMRI signals.

The dependency of the BOLD signal on the modulation frequency was investigated in an fMRI study by Giraud *et al.* (2000). They separated the transient and sustained response partials in several areas along the auditory pathway and found a clear response maximum at ~8 Hz for Heschl's gyrus. The frequency characteristic of the BOLD signal, showing the best responses at 8 Hz or below, is not consistent with that of the ASSR, which shows a broad range of responsiveness with a maximum at 40 Hz (Stapells *et al.*, 1984; Ross *et al.*, 2000). We assume that differences in modulation frequency might have different effects on lateralization. Further research is required to establish if a correlate of the 40 Hz ASSR can be seen in the BOLD signal. Consequently, we assume that the observed BOLD response and the ASSR do not correspond to each other and both types of activity reflect different underlying neuronal processes. The ASSR is a very small part of the electromagnetic activity and can be extracted from background noise by time domain averaging, because it is strongly phase-locked to the stimulus. The BOLD signal resembles the sum of responses that are both phase-locked and non-phase-locked to a stimulus. Thus, the BOLD signal corresponding to the ASSR might be hidden in larger BOLD signals corresponding to other response components. This view emphasizes the importance of combining results from different methods like MEG and fMRI.

RH Dominance for Pitch Processing

ASSRs follow the time-course of the AM stimulus envelope and represent the temporal structure of the sound. Therefore the question arises of how our RH dominance of the ASSR fits with the hypothesis, proposed by Zatorre and Belin (2001), that the LH auditory cortex dominantly processes fast temporal changes in sound whereas the RH auditory cortex dominantly processes the spectral fine structure of the sound. This question is related to whether acoustical features are encoded in the ASSR. At first glance, the ASSR might be related to the temporal structure of the stimulus. Another and probably more important perspective is to describe the ASSR as a response to sound periodicity. The importance of stimulus periodicity has been demonstrated by Ross and Pantev (2004), who have shown pronounced perturbation in the ASSR caused by violation of strict periodicity in the stimulus. Interestingly, both the ASSR and the SF are related to periodic sound structures, and thus it can be speculated that both may be relevant for pitch processing based on stimulus regularities, particularly in the RH. RH dominance for pitch processing was demonstrated by Zatorre (1988) in lesion

studies. Lesions to the right but not to the left PAC impaired the perception of a missing fundamental sound. The impairment was largest for missing fundamental sounds of higher frequency, in which the spectral components are not resolved in the auditory periphery and the perception of the pitch of the missing fundamental is based on the analysis of the temporal structure of the sound. Paquette *et al.* (1996) found more pronounced left ear advantage for pitch discrimination for missing fundamental sounds and concluded that there was RH dominance for the central pitch processor. Patients with right temporal lobe lesions could recognize in a two-alternative forced-choice test that two complex sounds were different; however, they failed to determine which sound had the higher pitch (Johnsrude *et al.*, 2000). Commonly, it was reported that lesions in the RH severely impaired pitch discrimination for complex sounds, indicating that areas in the right auditory cortex are involved in specific processing of complex sound.

Samson and Zatorre (1994) investigated the contribution of the left and right hemispheres to musical timbre discrimination. They compared the discriminatory ability for complex sounds with different spectral envelopes or different temporal envelopes between groups of patients with left or right temporal lobe lesions and healthy controls. The performance in spectral discrimination was superior to temporal discrimination in all groups, and patients with RH lesions were mostly impaired. In contrast to the hypothesis of LH dominance for temporal processing, patients with RH lesions were significantly more impaired in discriminating the temporal structure of sound. These results indicate that the right temporal lobe is involved in processing both spectral and temporal structures of sound, which are necessary for the recognition of musical timbre.

Missing RH Laterality in Secondary Auditory Cortex

Sources of 40 Hz ASSR were assumed to be present mainly in the PAC. Thus, the RH laterality of the ASSR provided evidence for the asymmetric representation of auditory information at the PAC level. Further processing in the non-PAC could be indexed by the N1m response, for which sources mainly in the non-PAC are assumed. However, in group results the N1 did not show any RH laterality in addition to the effect of contralaterality, and even the correlation between the LIs for the ASSR and N1m (Fig. 5) indicated that subjects with RH laterality for the ASSR showed a tendency to RH laterality for N1 also. An explanation for the lack of RH laterality in the group mean might be that the N1 response contains several components (Naatanen and Picton, 1987), which may be specific to differently stimulus attributes. However, it seems that the overall N1 response is a less sensitive indicator of hemispheric asymmetry. One reason for this difference is the larger inter-subject variability for N1m laterality than for the ASSR (Fig. 5). Rademacher *et al.* (2001) speculated that the degree of structural variability follows a hierarchical pattern, with primary cortical regions having smaller variations than the association cortices.

Conclusion

Right hemispheric laterality of the ASSR and SF was demonstrated in our study with amplitude-modulated tones, which carried no specific musical or speech information. This suggests that asymmetric representation of auditory information is already established at the level of sensory processing of complex sound. RH laterality was most pronounced in the

ASSRs, which are thought to reflect the periodical structure of the sound. ASSR laterality toward the RH might facilitate RH asymmetry for pitch processing based on the temporal periodicity of sound.

Notes

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