Stimulus Induced Desynchronization of Human Auditory 40-Hz Steady-State Responses

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Ross, B., A. T. Herdman, and C. Pantev. Stimulus induced desynchronization of human auditory 40-Hz steady-state responses. J Neurophysiol 94: 4082–4093, 2005. First published August 17, 2005; doi:10.1152/jn.00469.2005. The hypothesis that gamma-band oscillations are related to the representation of an environmental scene in the cerebral cortex after binding of corresponding perceptual elements is currently under discussion. One question is how the sensory system reacts to a fast change in the scene if perceptual elements are rigidly bound together. A reset of the gamma-band oscillation forced by a change in sensory input may dissolve the binding, which then would be re-established for the new sensation. We studied the reset of gamma-band oscillations on the 40-Hz auditory steady-state responses (ASSR) by means of whole-head magnetoencephalography (MEG). The rhythm of 40-Hz AM of a 500-Hz tone evoked the ASSR, and a short noise burst served as a concurrent stimulus. Possible direct interactions of the auditory stimuli were excluded by presenting the noise impulse in a different frequency channel (2,000–3,000 Hz) to the contralateral ear. The concurrent stimulus induced a considerable decrement in the amplitude of ASSR, which was localized in primary auditory cortices. This decrement lasted 250 ms and was significantly longer than the duration of the transient gamma-band response evoked by the noise burst. Thus it could not be explained by any linear superimposition of the responses. The time courses of ASSR amplitude and phase during recovery from the decrement resembled those after stimulus onset, indicating that a new ASSR was built up after the resetting stimulus. The results are discussed as reset of oscillations in human thalamocortical networks.

INTRODUCTION

Fast rhythmic changes in the electroencephalogram (EEG) or the magneto-encephalogram (MEG) with frequencies in the gamma-band may have a role in signaling feature binding in sensory systems (Bertrand and Tallon-Baudry 2000; Engel et al. 1992; Singer 1993). Although various definitions for the gamma-band were given in the literature using frequency limits between 20 and 100 Hz, the 30- to 60-Hz range seems to be most important for binding of sensory information (Singer 1993). The underlying hypothesis implies that the sensory system captures the environment in features like color, shape, orientation, and movement of a visual object and processes these in separate cortical areas (Felleman and Van Essen 1991). However, it is widely unknown how the feature binding is established and at which level in the sensory system (Shadlen and Movshon 1999). It has been suggested that gamma-band activity also plays an important role in a wide range of cognitive processes and that synchronous oscillation is a general principle of functional connectivity in the cortex (Kaiser and Lutzenberger 2003). However, we are still far away from unequivocally proving these concepts and any new experimental findings about oscillatory brain activity may contribute to the ongoing discussion.

Neural oscillations at specific frequencies result from firing properties of single neurons and from properties of reciprocal interactions between excitatory and inhibitory connections within networks of neurons. Rhythmic bursts of discharges in single neurons in neocortex and thalamus in cat showed high temporal correlation with depth electroencephalograph (EEG) recordings (Steriade 1997). Neurons with such intrinsic oscillatory properties may serve as pacemakers in thalamo-cortical networks (Llinas et al. 1991) with a wide frequency range of responsiveness (Gray et al. 1989). When the bursting neurons are embedded in a thalamo-cortical loop, as proposed by Llinas’ (2003) model, the network responds maximally at frequencies ~40 Hz. Several modulating inputs in the model allow the network to start and stop the rhythmic activity. Thus sensory input can reset the network, and the immediate restart after the reset then results in synchronized oscillatory activity, which can be recorded as mass activity in the EEG and magnetoencephalography (MEG) (Llinas and Ribary 1993).

The proposed stimulus induced reset of neuronal activity is an important concept at both the microscopic level of synchronizing oscillatory activity and at the macroscopic level of generating the event-related activity in the EEG and MEG. The latter is still under controversial discussion. For example, a stimulus induced reset of the phase, but not the amplitude, of the ongoing alpha (8–13 Hz) oscillation has been suggested as a fundamental mechanism for generating the event-related potential (ERP) (Sayers et al. 1974). The phase reset hypothesis was recently renewed by Makeig et al. (2002) for visual and by Jansen et al. (2003) for auditory ERPs. In contrast, the so-called “additive power” hypothesis suggests that a sensory stimulus evokes an additive neural response, which can be separated from the ongoing EEG by signal averaging (Hillyard 1985; Hillyard and Picton 1987; Jervis et al. 1983; Mangun 1992; Schroeder et al. 1995; Vaughan and Arezzo 1988). This latter view was supported recently by results of intracortical recordings in monkeys (Shah et al. 2004) and single-epoch analysis of human MEG (Makinen et al. 2005), demonstrating poststimulation signal power increase, whereas the hypothesis of pure phase reset requires equal signal power in pre- and poststimulus intervals.

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The investigation of the time course of induced oscillatory brain activities using the scalp-recorded EEG or MEG might be problematic or even not feasible because of their small amplitudes compared with the background activity. This problem may be overcome when studying steady-state responses, which are oscillations with constant amplitude and phase at the frequency of a periodic stimulus. The signal-to-noise ratio of steady-state responses can be enhanced by averaging in the time or frequency domain (John et al. 2001; Stapells et al. 1984) because of their strict phase locking to the eliciting stimulus. In the visual (Regan 1989) and auditory modality (Picton et al. 1987; Rees et al. 1986; Ross et al. 2000; Stapells et al. 1984), steady-state responses can be recorded with maximal amplitudes at stimulation frequencies ~40 Hz. Typical stimuli for eliciting auditory steady-state responses (ASSR) are sequences of clicks (Galambos et al. 1981; Hari et al. 1989), Gaussian tone pulses (Pantev et al. 1996), or amplitude-modulated tones (Picton et al. 1987; Rees et al. 1986). To study the temporal dynamics of 40-Hz ASSR, we addressed the question whether the ASSR is reset by a concurrent stimulus. If so, we could evaluate reset effects in human neural networks.

It has been previously reported that a concurrent stimulus induces modulation of the steady-state responses in several sensory modalities. In a series of experiments, Rohrbaugh et al. (1989, 1990a,b) investigated the effect of a single tone impulse on the amplitude and phase of 40-Hz ASSR, which was elicited by continuously presented tone pips. The main effect was a period of reduced ASSR amplitude immediately after the concurrent stimulus. In several EEG experiments Makeig and Galambos (1989) investigated stimulus induced ASSR perturbation and found an ASSR decrease after sudden shifts in the carrier frequency of tone pips between 1,000 and 1,200 Hz, a similar effect for a 6-dB intensity step of single pips or pairs of tone pips, no cross-modal effects between visual and auditory SSR. ASSR decrease is induced by a contra-lateral noise burst, and an ASSR decrease is induced by an omitted stimulus in sound sequence generating the ASSR (Makeig et al. 1992). In auditory odd-ball experiments superimposed on continuously presented 40-Hz tone pips, ASSR amplitude reductions lasting ~300 ms were found after standard and target stimuli and during the button press response to the target stimulus (Muller et al. 1994; Rockstroh et al. 1996). These changes in the ASSR were attributed to a brief interval of enhanced sensitivity caused by an orienting response to the concurrent stimulus (Rohrbaugh et al. 1989, 1990b). Rockstroh et al. (1996) interpreted their results as an indication that motor responses and processing of oddball stimuli alters auditory processing at the level of the primary auditory cortex.

In previous studies, we found that the time course of ASSR onset is characterized by changes in amplitude and phase lasting ~250 ms after stimulus onset (Ross et al. 2002). Furthermore, we found the same time courses for ASSR amplitude and phase alterations when a short gap was introduced into the AM sound (Ross and Pantev 2004). The present work continues and extends the depth of those studies with the following two objectives: to demonstrate stimulus-induced desynchronization of oscillatory brain activity in the human MEG using the 40-Hz ASSR and to investigate whether this desynchronization results from pure phase resetting or is accompanied by changes in the signal power. By means of whole-head MEG, we recorded cortical source activity and compared the time courses of ASSR decline after presentation of a concurrent stimulus with the time-course of ASSR after the onset of the ASSR eliciting stimulus. The working hypothesis was that the concurrent stimulus would introduce a reset of the ASSR, and the time courses of the changes in ASSR amplitude and phase during recovery would resemble those during the ASSR onset. The responses to separate monaural stimulation with the ASSR-generating AM sound and the concurrent stimulus were compared with responses to dichotic presentation of both stimuli to determine whether the response to dichotic stimulation could be explained by the sum of both monaural responses. In two further experimental conditions, the AM sound and the concurrent stimulus were combined and binaurally presented. It was expected that the single concurrent stimulus evoked a transient gamma-band response (tGBR) strictly time-locked to the stimulus. The tGBR and the ASSR could have the same phase, which would result in an amplitude increment of the combined response, or opposite phase, which would result in an amplitude decrement. In a second experiment, in which a violation of the periodicity of the AM stimulus itself served as concurrent stimulus, we addressed the question of whether the ASSR reset is a general reaction to a stimulus change.

**METHODS**

**Subjects**

The 14 subjects (5 female) who participated in the study were between the ages of 22 and 49 yr (mean: 33). Although no effect of handedness on the ASSR is known, a homogenous group of right-handed subjects was selected using the Edinburgh handedness questionnaire (Oldfield 1971). Hearing thresholds were <15 dB HL between 250 and 8,000 Hz. Informed consent was obtained from each subject. The experiments were part of a larger project entitled “Magnetoencephalographic Studies of Human Hearing,” which had received approval from the Research Ethics Board of the Baycrest Centre for Geriatric care. The subjects were paid for their participation.

**Auditory stimuli**

A sinusoidal AM tone of 800-ms duration with 500-Hz carrier and 40-Hz modulation frequency was used as the stimulus to elicit the ASSR (Fig. 1A). A brief burst of band-pass filtered noise (2,500 ± 500 Hz), with 5-ms half-intensity duration served as a perturbing stimulus (Fig. 1B). The noise burst was presented 400 ms after the beginning of the 800-ms AM sound, exactly centered at the minimum of the AM (Fig. 1C). The stimuli were presented in blocks of 250 same stimuli with an onset asynchrony (SOA) of 1.0 s, corresponding to an inter-stimulus interval (ISI) of 200 ms between succeeding AM sounds. Eight repetitions of the same stimulus block formed an experimental session of ~1-h duration. In three separate sessions, the AM sound was monaurally presented to the right ear, the noise burst was monaurally presented to the left ear, and the AM sound was presented to the right ear simultaneous with the noise burst presented to the left ear (i.e., dichotically). For binaural stimulation, the noise burst was adjusted so that it occurred either during the minimum (Fig. 1C) or during the maximum of the AM (Fig. 1D). In addition, 128 500-Hz tone bursts of 500-ms duration were presented with SOA of 2.5–3.5 s in two control measurements to obtain the auditory N1 responses. Eight subjects participated in the three sessions with monaural and dichotic stimulation, 11 in the two sessions with binaural stimulation of the first experiment, and 7 subjects in the second experiment. The individual sensation thresholds for the AM sounds were determined at the beginning of the experiment.
and noise sounds were determined at the beginning of each experimental session. The threshold for the short noise burst was, on average, 6 dB higher than for the AM sound. The stimulus intensity was set so that the AM sound was 60 dB above sensation level (SL). Consequently, the noise burst intensity was 54 dB SL. The stimuli were presented under control of STIM software (Neuroscan, Sterling, VA) using Etymotic ER3A transducers, which were connected via 1.5-m plastic tubes to silicon ear pieces fitted to the subject’s ears.

**MEG data acquisition**

MEG recordings 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. After low-pass filtering at 200 Hz, the magnetic field data were sampled at the rate of 625 Hz. Subjects were seated comfortably in upright position and were asked to remain alert. No instruction was given to the subjects regarding paying attention to the auditory stimuli because no effect of attention on the ASSR was expected (Linden et al. 1987). The subjects watched a self-selected soundless movie to control for confounding changes in vigilance. Compliance was verified using video monitoring. The visual stimulation was related to the course of the auditory stimuli, and no cross-modal effect on the ASSR has been found so far (Makeig and Galambos 1989; Rohrbaugh et al. 1990a). Head movements were verified to be <8 mm during each recording block using three detection coils attached to the subject’s nasion and both ear canals. No data had to be rejected because of head movements.

**Data analysis**

The data analysis was based mainly on the waveforms of source activity in the auditory cortices. MEG responses were modeled by single dipoles in left and right auditory cortex. Previous data analysis using a beamformer approach (Vrba and Robinson 2001) for source analysis, which does not need a priori assumptions about the source configuration, demonstrated that single dipoles are sufficient to describe the activation of the auditory cortex (Herdman et al. 2003). The magnetic field waveforms of cortical source activity \( q(r,t) \) are detected by each of the 151 sensors with a distinct sensitivity depending on the orientations and distances between the source and the sensors. If the sensitivities of all sensors at position \( R \) for the source activity at location \( r \) are given in matrix notation by the lead-field matrix \( L(r,R) \) (Sarvas 1987), the detected magnetic field \( B(R,t) \) can be described by \( B(R,t) = q(r,t) \cdot L(r,R) \). The pseudo-inverse of the lead-field matrix can be used to obtain the cortical source activity from the measured magnetic field: \( q(r,t) = B(R,t) \cdot L^{-1}(r,R) \). This operation, termed source space projection (Ross et al. 2000; Tesche et al. 1995), combines the 151 waveforms of magnetic field strength into a single waveform of a magnetic dipole moment measured in nanoAmper meter (nAmp). The dipole moment is most sensitive for the localized area in the brain and less sensitive to electromagnetic sources at other locations. Furthermore, averaging across independent sensors reduces the intrinsic sensor noise. Consequently, the method of source space projection results in waveforms with higher signal-to-noise ratio than the magnetic field waveforms (Ross et al. 2000). Another reason for analysis in source domain is that the dipole moment is independent of the sensor position. In general, the position of the subject’s head relative to the MEG sensor changes between sessions, and it is different between subjects as well. Combination of magnetic field data for group analysis is therefore not feasible. In contrast, the waveforms of cortical source activity can be combined across repeated sessions for a subject and across the group of subjects.

For each experimental block, the 250 stimulus-related epochs of the magnetic field data of 1,600-ms duration including 400 ms pre- and poststimulus intervals were averaged after rejecting artifact-contaminated epochs in which magnetic field changes >2 pT occurred. To increase the signal-to-noise ratio for the ASSR source analysis, the waveforms were averaged across all periods of the ASSR oscillation. Therefore the response waveforms in eight 50-ms intervals from 200 to 250 ms, 225 to 275 ms, and so on to the interval from 375 to 425 ms were averaged. Source analysis of the ASSRs was applied to the resulting averaged waveforms based on the model of spatiotemporal equivalent current dipoles (ECD) in a spherical volume conductor. Single 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. Dipole fits were accepted if the calculated field explained 90% of the variance of the measured magnetic field. Between 16 and 40 repeated estimates of two ECDs, one in each hemisphere, defined by their moment, orientation, and spatial coordinates, were obtained for each subject. Dipole localizations were accepted as reliable if in any Cartesian coordinate the SD obtained from repeated measurements was <8 mm. The mean of spatial coordinates and orientations were used as individual models for the ASSR. In the same way, the N1 responses were modeled for each subject by single dipoles in each hemisphere.

Single trial source waveforms were calculated based on the individual source estimates, averaged across all trials and repeated experimental blocks, and filtered using a 32- to 60-Hz band-pass to extract
the ASSR and the transient gamma-band responses (tGBR). The tGBR and ASSR sources were found to originate from overlapping areas in the primary auditory cortex (Ross et al. 2002), and therefore a common estimate for tGBR and ASSR sources was used. Time series of the transient P1-N1-P2 components and sustained responses were obtained from source-space projection based on the N1 source coordinates. The ASSR dipole amplitudes and latencies were measured as absolute values at the peaks in the ASSR waveforms using a customized MATLAB routine. To measure the latencies with better resolution than the sampling rate, the ASSR waveforms were interpolated on an eightfold finer time scale using the MATLAB resample function.

For time-frequency analysis, short-time Fourier transforms (STFT) were applied to single trial source waveforms using a Kaiser-window of 321-ms length (201 samples) and 512-point FFT with zero-padding. For a group analysis, the mean of coefficients and the mean power of coefficients were calculated across all trials and all subjects, which resulted in time-frequency representations of the averaged response (the evoked activity), the total signal power (evoked and induced activity), and the residual variance (signal power, which was not explained by the evoked activity). The time-frequency representations were normalized for visualization with respect to the mean amplitude spectrum, which was calculated from samples of the MEG source signal power during the prestimulus interval. The residual variance was normalized to a baseline estimate and visualized as percent change in amplitude. Additionally, the phase coherency was calculated for all time-frequency coefficients.

**RESULTS**

**Source localizations**

From magnetic source localization, which was performed as prerequisite for obtaining source waveforms, dissociation between ASSR and N1 sources was expected. N1 and ASSR source coordinates in both hemispheres were reliably estimated in all subjects. Relative to the N1 sources, ASSR sources were more medially located by 5.6 mm in the right hemisphere \[t(13) = 3.42, P = 0.005\] and by 7.2 mm in the left hemisphere \[t(13) = 4.17, P = 0.001\]. Differences in source coordinates in anterior-posterior direction and inferior-superior direction were not significant.

**Response waveforms obtained with the perturbing noise stimulus**

Waveforms of cortical source activity were analyzed to observe the effect of the perturbing noise burst stimulus on the ASSR amplitude. Clear auditory-evoked transient and steady-state responses were obtained from each individual subject under all experimental conditions. Examples of individual waveforms and the grand averaged waveforms of source activity in right auditory cortex are presented in Fig. 2. The 32- to 60-Hz band-pass filtered response in the top traces show that the brief noise stimulus, presented monaurally to the left ear, elicited a burst of tGBR lasting \(~50\) ms (Fig. 2A). Monaural presentation of the AM sound to the right ear elicited the ASSR. The ASSR time course showed four distinct intervals (Fig. 2B). 1) A tGBR appeared during the first 100 ms similar to the response that was elicited with the onset of the noise burst. 2) From 100 ms after AM sound onset, the amplitude of 40-Hz oscillations developed and increased almost linearly until it reached its maximum at \(250\) ms. 3) The constant 40-Hz amplitude between this time point and the end of the AM sound at \(800\) ms indicated a steady-state response. And 4) after the stimulus offset, the ASSR decayed within \(50\) ms. The sum of both monaural responses would be expected from dichotic stimulation if no interaction between the responses to both stimuli occurred. Such linear superimposition would predict an increment or a decrement in the oscillatory response after the noise burst depending on the phase relation between ASSR and the noise-induced tGBR. However, the decrement in ASSR amplitude after the perturbing noise burst was noticeably longer lasting than the duration of the tGBR evoked by the noise burst alone Fig. 2C. The detailed view in Fig. 2F demonstrates that the peaks of the noise burst response had almost opposite polarity than the ASSR response. Thus the hypothetical summation of the waveforms in Fig. 2, A and B, diminished the ASSR amplitude for about two cycles (Fig. 2G). However, the actual response to dichotically presented AM sound and perturbing noise was characterized by a fast decay during the 500- to 1000-ms interval.

**FIG. 2.** Response waveforms obtained from right auditory cortex of an individual subject (left) and averaged across the group (middle) band-pass filtered between 32 and 60 Hz (top traces) and 24-Hz low-pass filtered (bottom traces). A: monaural noise impulse presented to the left ear. B: monaural 40-Hz AM sound in the right ear. C: dichotic presentation of the AM sound to the right and the noise impulse to the left ear. D: binaural combination of AM sound and noise impulse inserted at modulation minimum. E: binaural stimulus with noise impulse at the AM maximum. F: section of responses to monaurally presented noise and AM sounds respectively. G: superimposition of responses to monaurally presented noise and AM sounds. H: overlay of responses to binaural stimulation with noise burst at AM minimum (thick line) and maximum (thin line).
decay of the ASSR and a 200-ms period of recovery from the decrement. Similar waveforms were obtained when the AM sound and the perturbing noise burst were combined and presented binaurally (Fig. 2D). With binaural stimulation, the ASSR and tGBR amplitudes were in general larger than those obtained with dichotic stimulation. However, the effect of the perturbing noise burst on the ASSR time course resembled that observed with dichotic stimulation. Shifting the noise burst relative to the AM sound by half a cycle (12.5 ms) should result in an amplitude enhancement if the responses to AM sound and noise burst were superimposed without any interaction because peak amplitudes of both response signals occurred simultaneously with the same polarity. However, the opposite effect was observed. The ASSR amplitude decreased and again it needed 200 ms for recovery to the steady state (Fig. 2E). The overlay of response waveforms to both binaural stimuli, shown in Fig. 2H, demonstrates a larger response during an interval of 1.5 AM cycles (<40 ms) in case of the tGBR and the ASSR being in phase. However, the response amplitude was never larger than the steady-state amplitude before and after occurrence of the perturbing stimulus.

The 24-Hz low-pass filtered response waveforms are shown in Fig. 2, bottom traces. The brief noise burst presented monaurally to the left ear elicited a P1-N1-P2 response. The onset of the right ear AM sound resulted in a similar P1-N1-P2 complex followed by the sustained response, which lasted for the duration of the AM sound (Fig. 2B). In the case of simultaneously presented AM sound to the right ear and a noise burst to the left ear, the low-pass filtered response waveform resembles the superimposition of responses to separate monaural stimulation with both stimuli (Fig. 2C). The response contains the P1-N1-P2 complex at AM onset, the sustained response, and a superimposed second P1-N1-P2 complex after 400 ms elicited by the noise pulse. The response components to combined dichotic stimulation were generally smaller than to separate monaural stimulation. The response to binaural stimulation was similar to the response obtained with dichotic stimulation (Fig. 2D). The P1-N1-P2 complex after 400 ms was smaller when the noise burst occurred simultaneously at the AM maximum than at the AM minimum (Fig. 2E).

Time course of response phase

The latency of the ASSR, with respect to the AM stimulus, was studied in detail to compare the time courses of deviations induced by the perturbing stimulus with those of the ASSR onset. Close similarity between both responses would be interpreted as a new onset after the induced perturbation. Deviations from the steady state, during which the response phase and amplitude were constant, were measured as latency differences between corresponding maxima of the ASSR and the AM sound. The time courses of the mean latency differences across the groups are shown in Fig. 3. Because the absolute ASSR latency is ambiguous by multiple periods of the 40-Hz stimulus (i.e., 25 ms), the mean ASSR latency was set to zero in the steady-state interval 200–400 ms after onset of the AM stimulus. Immediately after onset of the monaurally presented AM sound (Fig. 3A) the response latency was shorter than in the steady state as indicated by a negative latency difference. This latency difference was ~6 ms at 100 ms after the stimulus onset, which corresponds to one-quarter of the modulation cycle or a 90° phase difference. The latency increased almost linearly with increasing time until reaching the steady state. Similar latency time courses were observed for the dichotic presentation of AM sound and perturbing noise burst (Fig. 3B) and the binaural stimulation with the noise at AM minimum (Fig. 3C) and at the AM maximum (Fig. 3D). We defined the beginning of the steady-state interval as the time when the latency difference was not significantly different from zero. These time points, in the postonset range between 253 and 312 ms (mean: 282 ms), are indicated by circles in Fig. 3. No significant latency differences were found between the left and right hemisphere. The concurrent stimulus at 400 ms also induced a latency decrease, which was maximal ~100 ms after

![FIG. 3. Time courses of latency shifts between auditory steady-state responses (ASSR) and 40-Hz AM of the stimulus in the responses obtained from left and right auditory cortex. The thick lines represent the group mean and the gray shaded area the 95% confidence interval of the mean. The circle symbols denote the beginning of steady-state interval, in which the latency difference is not significantly different from zero. A: Monaural 40-Hz AM sound in the right ear. B: dichotical presentation of right AM sound and left noise impulse. C: binaural combination of AM sound and noise impulse inserted at modulation minimum. D: noise impulse at modulation maximum.](http://jn.physiology.org/)

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the noise pulse. The averaged latency shift across the group at this time was 3–4 ms. The latency increased with increasing time and the steady state recovered on average at 230 ms after the occurrence of the noise burst.

Violation of stimulus periodicity

The second experimental study addressed the question of whether a stimulus in a different sensory channel is necessary to induce the observed ASSR perturbation or if a change in the ASSR eliciting stimulus is sufficient. Therefore a sudden change in the periodicity of the AM sound was used as a perturbing stimulus. An 180° phase shift was introduced to the AM sound by extending the AM maximum by 12.5 ms (Fig. 4A) or extending the slope of the modulation signal by the same amount of time (B). The ISI was shortened to 1.5 AM cycles (37.5 ms), corresponding to a SOA of 825 ms. The resulting stimulus sequences can be described as continuous AM sound with repeated disturbances by gaps of 37.5 ms and phase shifts of 12.5 ms. The obtained response waveforms are shown in Fig. 4, bottom. The ASSR time courses show characteristic decreases in amplitude for both the gap of 37.5 ms between succeeding AM sounds and for the phase-shift at 400 ms. In both cases, the recovery after amplitude decrement lasted for ~200 ms. The time courses of ASSR amplitudes obtained with nondisturbed AM sound are compared in Fig. 5 with those obtained with AM sounds containing periodicity violations. Responses to both types of periodicity-change stimuli and responses obtained in left and right hemisphere were averaged to improve the signal-to-noise ratio. The amplitude time courses showed a characteristic decrement and ~200 ms lasting recovery both after the gap and also after the phase shift. After onset of the nondisturbed AM sound, the ASSR showed significant facilitation of the amplitude in the 200- to 300-ms time interval. A similar but smaller overshoot is also visible during ASSR recovery 200–300 ms after the phase change stimulus (i.e., 600–700 ms after AM sound onset). This overshoot, however, did not reach significance in the group statistics. The initial amplitude overshoot complicates the exact determination of the beginning of the steady-state interval, which can be obtained more accurately from the time courses of the response latency in Fig. 5, E and F. The time course of ASSR latency showed a 12.5-ms step corresponding to the phase step in the AM stimulus. Before the steady-state latency was reached, the latency increased linearly over a 200-ms interval with a similar slope as seen during the response onset. The response reached the steady state 258 or 267 ms after stimulus onset and 234 ms after the periodicity change stimulus, respectively (Fig. 5, E and F).

Analysis of response signal power

The response signal power was analyzed in a group analysis to determine whether the observed reset is a pure phase effect or is accompanied by a modulation of the response power. Time-frequency representations of grand averaged source activity in left and right auditory cortex are shown in Fig. 6. The evoked responses (Fig. 6, A–D) were normalized with respect to the averaged spectral amplitudes across the prestimulus interval (Fig. 6G). The evoked response to the noise burst stimulus (Fig. 6A) exhibits low frequency activation between 450 and 650 ms, corresponding to the P1-N1-P2 complex, and a short interval of activation in a broad frequency range immediately after the stimulus, corresponding to the tGBR. The responses were larger in the right hemisphere, contralateral to the stimulated left ear. The horizontal bands at 40 and 80 Hz in Fig. 6B denote the 40-Hz ASSR and the first harmonic of the ASSR elicited by the AM sound. The ASSR amplitude

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![Image](https://via.placeholder.com/150)

**Fig. 4.** Top: time series of AM stimuli containing periodicity violations. Left: current stimulus in full length (filled graph) and its preceding and succeeding stimuli (open graphs). Right: section of the stimuli around 400 ms on enlarged time scale. A: 40-Hz amplitude modulated 500-Hz tone-burst of 800-ms duration with ISI equivalent to 1 omitted AM period of 25 ms and an 180° phase shift after 400 ms. The phase shift was introduced by holding the AM envelope for 12.5 ms at its maximum. B: stimulus like A with the phase shift introduced by extending the rising slope of 1 AM period by 12.5 ms. Bottom: response waveforms obtained from right auditory cortex of an individual subject (left) and averaged across the group (right) obtained after a 37.5-ms gap in the stimulus (at t = 0) and after 180° phase shifts at (400 ms). C and D: between 32- and 60-Hz band-pass filtered responses to stimuli A (C) and stimuli B (D). E and F: 24-Hz low-pass filtered response corresponding to C and D.
was larger in the right hemisphere even though this is ipsilateral to the stimulated right ear. The ASSR shows an amplitude overshoot in the response obtained from the left hemisphere. Similar bands of ASSR can be seen in Fig. 6C in the response to dichotic presentation stimulation with the AM sound and perturbing noise burst at 400 ms. The band of 40-Hz activity is clearly disrupted after 400 ms. Similar disruption of 40-Hz perturbing noise burst at 400 ms. The band of 40-Hz activity is important to dichotic presentation stimulation with the AM sound and perturbing noise burst. The band of 40-Hz activity is important to understanding the mechanisms of ASSR.

**Discussion**

A brief noise burst concurrently presented with continuous AM sound evoked a substantial reduction in ASSR amplitude, even though both stimuli were in different frequency bands and presented to different ears. Moreover, a change in the periodicity of the AM stimulus itself disrupted the ASSR. The time courses of ASSR amplitude and phase during recovery from the perturbation resembled those obtained after the stimulus onset. The change in the ASSR time course induced by a perturbing stimulus thus denotes a new stimulus onset after reset of activity. Our experimental results should be viewed in the context of the results from previous studies. Although, we generally found broad consistency, our results allow a new interpretation. First, we discuss our results as further evidence that the ASSR is an independent type of brain activity that does not result from periodic superimposition of transient auditory-evoked responses. Second, we discuss our results as demonstration of a central mechanism for maintaining high temporal acuity during temporal integration over several hundreds of milliseconds.

Because individual magnetic resonance images were not available for all subjects, we could not assign the source coordinates to anatomical structures. However, the clear separation between more medial ASSR sources and more lateral N1 sources was taken as evidence for ASSR sources in primary auditory cortex, and N1 sources in nonprimary auditory cortex. This is consistent with previous results from simultaneous recordings of both response types (Engelien et al. 2000; Herdman et al. 2003; Pantev et al. 1996; Ross et al. 2002). Furthermore, several observed features of the ASSR perturbation are...
also in line with observations from previous studies (Makeig and Galambos 1989; Muller et al. 1994; Rohrbaugh et al. 1989, 1990a), namely the 200- to 300-ms poststimulus decrease in the ASSR amplitude, and the 4- to 6-ms decreased ASSR latency, which occurs before a return to the steady state. The ASSR perturbations were discussed as reflecting a period of sensitization that occurs at an early level in the auditory system, during orienting to the concurrent stimulus (Rohrbaugh et al. 1989, 1990a,b), as suppression of the ASSR during the generation of slow wave responses (Muller et al. 1994) and as an effect of attention (Makeig 1993). However, in those studies the time course of ASSR recovery from the decrement was not compared with the ASSR onset. The results of such comparison, presented here, permit a discussion of the time courses of amplitude and phase during recovery in relation to a new ASSR onset after a stimulus-induced desynchronization of the ASSR.

Makeig and Galambos (1989) already reported that the ASSR perturbation, induced by an omitted click in their stimulus series, could not be explained using the transient response to a single click. We extensively investigated the possibility that our results could be explained by the superimposition of different responses. The summation of single monaural responses did not explain the response to simultaneous presentation of both stimuli. The monaural AM stimulus elicited a 40-Hz ASSR continuing for the duration of the AM sound, and the short noise burst evoked almost two cycles of gamma-band oscillations. The responses were mainly of opposite polarity, and a summation resulted in an amplitude decrement of the ASSR. However, the effect of dichotic stimulation empirically showed 200- to 300-ms perturbation of the ASSR, which was much longer than the effect of response superimposition. Furthermore, shifting the noise burst by half a period to align the ASSR and the tGBR to equal polarity did not result in an

FIG. 6. Time-frequency representation of grand averaged responses obtained from left and right auditory cortex. A: amplitude of source activity evoked by left ear noise impulse normalized to the averaged spectral amplitude shown in G. B: evoked activity to the right ear AM sound. C: dichotic presentation of right AM sound and left noise impulse. D: binaural combination of AM sound and interacting noise impulse. E: phase coherence obtained with binaural stimulation. F: partial of averaged signal power, which is not explained by evoked activity, in percentage change compared with the prestimulus interval. G: mean spectral amplitude in left and right auditory cortex. H: examples of 40-Hz phase distribution in a prestimulus interval (~10 ms), after ASSR onset (230 ms), during stimulus induced perturbation (470 ms), and after recovered ASSR (630 ms).
amplitude increase over the steady-state amplitude evoked by the AM-stimulus alone. However, the ASSR decrement was smaller when the single responses were in phase (i.e., the noise pulse was presented at the AM maximum) compared with out-of-phase responses (i.e., the noise pulse was presented at AM minimum). The superimposition of both types of binaural responses showed a substantial difference for a time interval equal to the duration of the noise burst response. These results are interpreted as showing two overlapping effects of the perturbing noise burst, a decrement in the ASSR and a superimposed tGBR. We did not observe an amplitude enhancement under any stimulus conditions. The ASSR decrement was always more strongly expressed than the tGBR. Thus we conclude that the stimulus-induced ASSR perturbation denotes a strong interaction between the ASSR and the response to the interfering stimulus. This is noticeably different from the superimposition of the single responses.

The time course of latency decrease at stimulus onset and ASSR perturbation provided further insight into the mechanisms of ASSR generation. A consistent experimental result was the decrease in ASSR latency induced by the perturbing stimulus. During recovery, the ASSR latency increased with the same temporal dynamic seen during the ASSR onset. The range of latency shift was ~5 ms for the stimulus onset and 3–5 ms for the response recovery. This is consistent with our previously reported latency shifts of 3–4 ms during ASSR onset (Ross et al. 2002) or after recovery from ASSR perturbation induced by a gap in the AM stimulus (Ross and Pantev 2004). Furthermore, the latency shift is consistent with the 4.5–6 ms reported by Rohrbaugh (1989, 1990a, b) and ~3.3 ms as was reported by Muller et al. (1994). All reported latency shifts correspond to a phase shift of ~60–90° at 40 Hz. With laminar recording using a linear array of 16 electrodes in cat primary auditory cortex, Sukov and Barth (1998) identified supra- and infra-granular sources of 40-Hz activity and measured a latency difference of 6 ms between both. Their interpretation was that the two sources reflect rhythmic interaction in a driven oscillatory network. The latency difference of 6 ms corresponds to the optimal phase difference of 90° in a simple oscillator. Such a model is certainly oversimplified. However, the consistency of phase shifts observed in different studies is striking and gives rise to an explanation of the effect in terms of tuned oscillatory networks. The ASSR phase during the steady-state intervals may correspond to the phase in a resonance state. A hypothetical driving source would have a 6-ms shorter latency. The ASSR phase immediately after stimulus onset would correspond to the phase of the driving source and would shift during the 200- to 300-ms onset to the resonance phase. The perturbing stimulus would reset the oscillations and shift back the ASSR phase to the phase of the driving source. Such a model was supported by a recent MEG study (Bish et al. 2004), in which two sources for the ASSR were identified in the auditory cortex and medial geniculate nucleus of the thalamus with the thalamic source oscillations leading the cortical source by 6 ms.

In summary, our results provide strong support for classifying the ASSR as a type of stimulus-driven oscillatory brain activity rather than an evoked response. In a review article, Bertrand and Tallon-Baudry (2000) classified oscillatory gamma-band activity in humans into both evoked and induced responses and added the steady-state response as a third class. This ambiguity characterizes the ongoing discussion about the nature of the ASSR. Originally it was suggested that the ASSR results from periodic superimposition of middle latency responses (Galambos et al. 1981). Several experimental results were not compatible with the concept of superimposed evoked responses. For example, superimposed evoked responses could not explain either the time course of ASSR onset (Ross et al. 2002) or the frequency characteristics of ASSR (Santarelli and Conti 1999). The long-lasting ASSR perturbation that was induced by the omission of a single click, in a series of 40-Hz click stimuli, also could not be explained by superimposition of the response to a single click (Makeig and Galambos 1989). Consequently, we favor the hypothesis that the ASSR is more
likely induced activity, which is facilitated by the rhythmic stimulation with frequencies close to the best responding frequency of the underlying neural network.

When studying the nature of the ASSR time course, the changes in 40-Hz signal power might provide insight into the question of whether the ASSR is caused by phase resetting of the ongoing gamma-band activity or by additionally synchronized activity. The hypothesis supporting a pure “phase reset” requires that signal power does not change between the pre- and poststimulus interval (Shah et al. 2004). However, we found an increase in total 40-Hz power after the AM stimulus onset, a temporary decrease after the concurrent stimulus, and a decrease to baseline power levels after the AM stimulus offset. The finding of a power increase, during 40-Hz AM stimulation, suggests that the ASSR is generated in addition to ongoing spontaneous activity. The requirement for accepting the hypothesis of a “pure phase resetting mechanism” without any power increase is not fulfilled here. However, the discussion is not completely satisfying because a mixed effect of phase resetting and an increase of induced activity cannot be excluded. Interestingly, the increase in 40-Hz power was even larger than the power found in the phase-locked ASSR activity. The increase in power, due to nonphase locked changes, could be considered as a stimulus-induced response. A more reasonable explanation is that the amplitude of the averaged ASSR was underestimated due to phase variation over time. Therefore we presently assume that the stimulus-induced change in 40-Hz variance was likely part of the ASSR. On the other hand, the very small amount of variance demonstrates that ASSRs are astonishingly well time-locked to the AM stimulus. No evidence exists for larger ASSR power than the change in total 40-Hz signal power. Overall, the results tend to support the hypothesis of separate neural oscillation, in addition to ongoing brain activity, as the generation mechanism for the ASSR. The perturbing stimulus induced a clear decrement of the total oscillatory activity and represents a mechanism different from pure phase reset mechanism as proposed elsewhere (Makeig et al. 2002). The desynchronization of ASSR described in this study is associated with partial or complete decrease of the amplitude of oscillatory signal power back to the prestimulus baseline.

Another central result was that a discontinuity in the AM sound, which was used to generate the ASSR, caused an ASSR desynchronization that was similar to that observed with an additional noise burst. This was true independent of whether the stimulus contained a signal power decrease (in case of a gap), signal power increase (in case of extended plateau time), or no signal power change (in case of the prolonged rising slope). The ASSR phase followed the phase shift in the stimulus. However the characteristic time course of an ASSR onset was superimposed. Furthermore, stimulus phase shifts evoked P1-N1-P2 responses similar to the responses evoked by the AM sound onset or the short noise burst. All stimuli and stimulus changes were clearly above detection thresholds. The auditory system detects both the concurrent stimulus and the stimulus change. The subsequent auditory processing is reflected by both the transient responses and by the ASSR desynchronization. The “onset” and the “change” responses reflect clearly different processes. In the latter response, a memory is involved, whereas this is not the case for the response to stimulus onset. It is not known which neural structures initiate these responses. However, so far, the experimental results indicate that the ASSR desynchronization is a general reaction to both a new stimulus and a stimulus change.

In earlier studies we interpreted the onset of ASSR, lasting for ~200–300 ms after stimulus onset, as reflecting temporal integration in the auditory system (Ross and Pantev 2004; Ross et al. 2002). Temporal integration with time-constants of several hundred milliseconds was demonstrated in psychoacoustics with lower hearing thresholds for sounds of increased duration (Gerken et al. 1990; Green et al. 1957; Plomp and Bouman 1959). On the other hand, the models for gap detection of a noise stimulus required integration time constants of ~3 ms (Buus and Florentine 1985). Thus the time constants responsible for temporal resolution and temporal integration differ by about two orders of magnitude. However, it is unlikely that the brain uses multiple structures in parallel, with different time constants for temporal integration and temporal acuity. This discrepancy was termed the “integration-resolution paradox” (deBoer 1985). Viemeister and Wakefield (1991) attempted to resolve this paradox with the model of “multiple looks” and hypothesized that the auditory system acquires short samples of the acoustic signal at high rates. These samples are stored in parallel, and the temporal integration is realized through combination of samples without the need of a long integration time constant. This attempt noticeably improved the modeling of temporal auditory processing. However, this model was not able to explain a number of experimental observations. For example, Plack and White (2000) found higher-pitch discrimination thresholds for two complex tones of 20-ms duration, which were separated by 8 ms, than for a 40-ms burst of the same complex sound. However, when the 8-ms gap was filled with noise of the same spectral range as the complex tone, the two 20-ms bursts were perceived as a continuous tone, and a lower-pitch discrimination threshold was found. This experimental observation was interpreted as evidence for temporal integration in pitch discrimination, which was reset, if a discontinuity in the sound occurred. Hafer and Buell (1990) demonstrated in psychoacoustical experiments that a stimulus change, or a concurrent stimulus, could prevent the binaural processing system from showing adaptation. Adaptation is an effective mechanism, which prevents the central processor from overload with irrelevant input. However, the reduced sensitivity in an adapted sensory channel becomes a disadvantage when fast reactions to environmental changes are required. A reset from adaptation can overcome this disadvantage. Rogers and Bregman (1998) described a reset of stream segregation in auditory scene analysis. Their interpretation was that sensitivity to sudden stimulus change prevents the auditory system from accumulating data across unrelated events. These psychoacoustic studies demonstrated that time-continuous models could not sufficiently describe auditory system performance. The introduction of a time-discontinuous reset was helpful. Our electrophysiological results provide an example of the existence of massive reset mechanism in macroscopic neuronal networks. The present experimental results corroborate and extend previous observations of ASSR reset after a gap in the AM stimulus (Ross and Pantev 2004). The variety of stimulus conditions, which induced ASSR reset in the present study, may emphasize the idea that a reset can be caused by rather general change detection and does not require a specific stimulus.
Stimulus-induced desynchronization of gamma-band oscillation in the visual cortex of cat has been shown by Kruse and Eckhorn (1996). In their study, a slowly moving grating pattern generated ongoing oscillations in the 35- to 80-Hz range and sudden acceleration of the movement evoked stimulus-locked transient responses. Increasing the stimulus intensity increased the transient response and degraded the oscillatory response, which was finally completely suppressed. The gamma-band oscillations were discussed as being related to perceptual binding. However, oscillations lasting several hundred milliseconds may be disadvantageous for the perception of fast-changing scenes (Gray et al. 1992). Thus Kruse and Eckhorn (1996) interpreted their observation of stimulus induced inhibition of gamma-band oscillations as a mechanism that allows fast processing of changing visual input even when previously perceptual elements were bound to a more static percept. This discussion parallels our interpretation that a stimulus-induced desynchronization may reflect a neural mechanism to overcome the problem of temporal integration versus temporal resolution.

The disruptive stimuli in our study were above detection thresholds. Thus we did not show how much change is necessary to disrupt the ASSR. It is reasonable to a more fainter noise burst, or a slight change in the stimulus phase, would not reset the ASSR. In a previous study, we observed a partial reset of the ASSR when the duration of a gap in the AM decreased (Ross and Pantev 2004). Perturbations of the ASSR were detectable for gap duration as small as 3 ms, corresponding to a phase shift of \(~45^\circ\).

Another open question is whether the ASSR could be reset by a stimulus in a different sensory modality. The results of previous studies are inconsistent. Rohrbaugh et al. (1990a) demonstrated perturbation of the ASSR induced by a visual flash, whereas Makeig and Galambos (1989) showed perturbation of auditory and visual steady-state responses only with stimuli in the same modality. We suspect that the cross modal reset of steady-state responses, if it exists, is a much smaller effect than the within modality reset demonstrated in our study.

Conclusions

The stimulus-induced desynchronization of rhythmic brain activity as demonstrated with the MEG may serve as a model for studying reset phenomena in oscillating networks in humans. The temporal dynamics of the ASSR amplitude and phase gave further insight into its generation mechanism. These dynamics also led us to classify the ASSR as an induced oscillation, which is facilitated by the rhythmic stimulation at best responding frequencies of the underlying neural network.

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