Human Auditory Steady-State Responses: The Effects of Recording Technique and State of Arousal

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There is some controversy in the literature about whether auditory steady-state responses (ASSRs) can be reliably recorded in all subjects and whether these responses consistently decrease in amplitude during drowsiness. In 10 subjects, 40-Hz ASSRs became significantly different from background electroencephalogram activity with a probability of $P < 0.01$ and an average time of 22 s (range, 2–92 s), provided that the responses were analyzed with time-domain averaging rather than spectral averaging. In a second experiment with 10 subjects, 40-Hz ASSRs recorded between the vertex and posterior neck consistently decreased in amplitude during drowsiness and sleep. Findings that the ASSR may occasionally increase during drowsiness may be explained by postauricular muscle responses recorded from a mastoid reference. These may occur during drowsiness in association with rolling-eye movements. ASSRs recorded between the vertex and posterior neck are not distorted by these reflexes. These findings combine with previous literature on the effects of general anesthetics on the ASSR to confirm that the ASSR is a valid option for monitoring the hypnotic effects of general anesthetics.

(Anesth Analg 2003;97:1396–1402)

The auditory steady-state response (ASSR) is the electrical response of the brain to regularly repeating auditory stimuli. Attenuation of the 40-Hz ASSR provides a sensitive marker of anesthesia (1–4), comparable to the bispectral index of the electroencephalogram (EEG) (5) and other measurements of the auditory evoked potential (6). Pockett and Tan (7), however, recently reported that many alert subjects did not display easily recordable ASSRs, prompting them to doubt that the ASSR could be used as a routine monitor of anesthesia. Our study attempted to resolve the controversy raised by these findings.

Pockett and Tan obtained a power spectrum for each of 10 2-s EEG epochs and then averaged these spectra. We hypothesized that their inability to record significant ASSRs was caused by their unusual averaging procedures. Averaging power spectra without considering phase does not improve the signal-to-noise ratio (SNR). We therefore compared spectral averaging with the usual procedure of time-domain averaging.

Pockett and Tan also reported that the amplitude of the ASSR sometimes increased during drowsiness induced by alcohol. This finding differs from the widely reported decrease in the 40-Hz ASSR with sleep (8–10). We hypothesized that their increased responses were caused by postauricular muscle responses (PAMRs) (11–13). To evaluate this hypothesis and to confirm that the ASSR consistently decreases during drowsiness and sleep, we recorded multichannel ASSRs while subjects fell asleep naturally.

Methods

This research was approved by the Research Ethics and Scientific Review Committee at the Baycrest Centre. All subjects provided written, informed consent.

Ten subjects (age, 23–47 yr; 5 women) participated in the first experiment, and 10 subjects (age, 22–36 yr; 3 women) in the second. The subjects sat in a comfortable reclining chair in a sound-attenuated chamber. For the first study, the subjects watched a movie played silently with subtitles. For the second experiment, the subjects came to the laboratory the day after sleeping 1–4 h less than their normal duration. During wakefulness, we recorded the ASSRs with the eyes

Funded by the Canadian Institutes of Health Research.
Accepted for publication June 5, 2003.
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DOI: 10.1213/01.ANE.0000082994.22466.DD

0003-2999/03

looking left or right as well as straight ahead, because these manipulations enhance the PAMR (14). The subjects were allowed to fall asleep naturally.

The stimuli were 1-kHz tonebursts with a total duration of 5 ms and rise/fall times of 2 ms. For the first experiment, the stimuli were created by using the MASTER system (15) and presented binaurally through Etymotic 3A insert earphones. Intensities (expressed to the nearest 5 dB) were calibrated with a Brüel and Kjaer 2230 sound level meter with a 2 cc DB 0138 coupler. The average perceptual threshold for these stimuli (presented monaurally) was 25-dB peak sound pressure level (pSPL). In the first experiment, the stimuli occurred at five different rates (32, 40, 50, 64, and 80 Hz) and three intensities (60-, 75-, and 90-dB pSPL). Each of the 15 stimuli (5 rates and 3 intensities) was presented for 160 s.

For the second experiment, the stimuli were presented at a 75-dB pSPL by using rates of either 40 or 80 Hz. The stimuli were created with a Tucker Davis RP2 processor. The stimuli were presented for 100 s.

For the first experiment, a single channel of EEG was recorded between electrodes placed at the vertex and the posterior midline neck just below the hairline. The EEG was amplified and filtered (1–100 Hz) with a Grass P55 amplifier and digitized (6 nV per bit) at 500 Hz. The same clock controlled both the analog-digital conversion and the timing of the stimuli.

For the second experiment, recordings were obtained with a Neuroscan Synamp system (30 nV per bit; 500 Hz; bandpass, 0.1–100 Hz) from nine electrodes referred to the posterior neck. Three channels monitored eye movements: one at each lateral canthus and one above the left eye. Six channels monitored the EEG: vertex, left and right central regions, left and right mastoids, and occiput. The stage of arousal was classified (16,17) as waking (eyes open), waking (eyes closed), drowsy or Stage 1 sleep (rolling-eye movements, fragmentation of the α rhythm, and increased θ activity), Stage 2 sleep (spindles and/or K-complexes), Stage 3 sleep (20%–50% δ), and Stage 4 sleep (more than 50% δ activity).

The EEG data were analyzed on the basis of contiguous 2-s epochs (containing exactly 1000 data points). A discrete Fourier transform provided the amplitude and phase delay of the response at the frequency of stimulation. The SNR was assessed by using the F ratio of the power at the stimulus frequency to the average power in the five bins immediately above and below this frequency (15).

To demonstrate the differences between spectral averaging and time-domain averaging, we evaluated eight epochs for each subject in all conditions of the first experiment and during drowsiness or sleep in the second experiment. For "spectral averaging," we averaged the amplitude spectra from each of the 2-s epochs (without considering phase). For "time-domain averaging," we averaged the time-domain data and then computed the amplitude spectrum. This would be equivalent to averaging the real and imaginary coefficients and then recomputing the amplitude spectrum, or "coherent" spectral averaging (18). Finally, we determined the effect of increasing the time over which the spectrum was calculated by concatenating the recordings and computing the spectra over the longer epochs ("long-time spectra"). The resolution of the spectrum changed from 0.5 Hz for a 2-s epoch to 0.0625 Hz for a 16-s epoch.

In the first experiment we assessed the SNR after each 2 s of time-domain averaging. For each rate and intensity and for each subject, we measured the time when the probability first went below 0.01. In the 9 of 150 cases in which the response did not become significant within 160 s, we estimated the time by extrapolation. These times were evaluated after logarithmic transformation by using a repeated-measures analysis of variance (ANOVA). The amplitudes and phases of the responses (as measured by time-domain averaging after 160 s) were evaluated by using a two-way (intensity versus rate) repeated-measures ANOVA.

ASSRs were measured over periods of 100 s by using time-domain averaging in each of the states of arousal. Response amplitudes were measured both in nanovolts and as a percentage of the amplitude in the initial waking recording for that subject. Because recordings were not available for all subjects in all sleep states, we collapsed the data over the states of drowsiness and light sleep (Stages 1 and 2) and used an ANOVA with three conditions (waking before drowsiness, drowsy or asleep, and waking afterward).

Several subjects showed prominent PAMRs on sustained lateral gaze (6). In the subject with the largest response, we evaluated the mastoid and vertex recordings during drowsiness with and without rolling-eye movements.

Results

Figure 1 shows the results of the three different analyses in a single subject. Time-domain averaging and long-time spectra decreased the amplitude of the background noise and increased the SNR. Spectral averaging did not decrease the mean amplitude of the background noise but decreased the variability in the spectrum from one frequency to the next. For the 10 subjects, the average F ratio for the first 2-s epoch of the 40-Hz stimulus at the 75-dB pSPL was 4.8. After 16 s, this became 4.3 for spectral averaging, 34.8 for time-domain averaging, and 28.3 for long-time spectra. Table 1 presents the number of significant responses (at $P < 0.01$) after 16 s for each of the three techniques. Similar results were obtained for the data

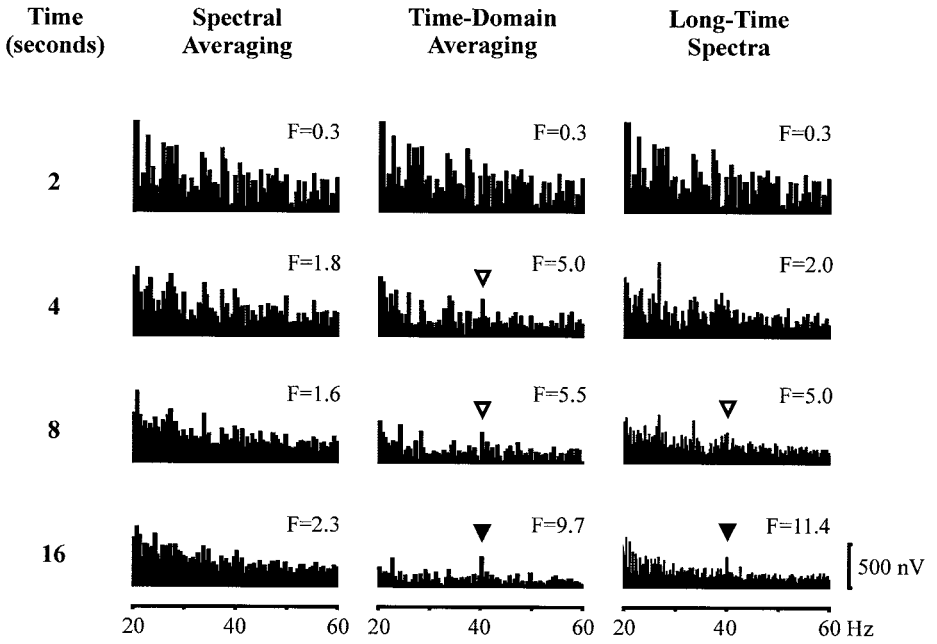

Figure 1. Detecting auditory steady-state responses. This figure shows the responses to 75-dB peak sound pressure level tones presented at 40 Hz to one subject. Data over 16 s were analyzed with three different techniques: spectral averaging, time-domain averaging, and long-time spectra. Amplitude spectra are shown between 20 and 60 Hz. The F ratios from comparing the power at the signal frequency with the power in adjacent frequencies are given with each recording. With 2 and 20 *df*, F values of 3.49 and 5.85 were significant at $P < 0.05$ and $P < 0.01$, respectively. The width of frequencies over which the noise was estimated decreased with increasing time in the long-time spectra (i.e., the number of bins remained constant). ▽Significant at $P < 0.05$; ▼ significant at $P < 0.01$. The spectra after 2 s were the same across the three analysis techniques because the base epoch was 2 s. With increasing time, only time-domain averaging and long-time spectra reduced the noise and led to an increased signal-to-noise ratio (reflected by increasing F ratios). Long-time spectra also increased the frequency resolution (i.e., the spectral lines or bins became finer as the duration of recording increased). As more data were collected, spectral averaging did not reduce the average level of the noise but simply made the spectrum smoother.

recorded during sleep and drowsiness in the second experiment. After 2 s, 20% of the 40-Hz responses were significant at $P < 0.01$ (average F ratio, 3.5). After 16 s, with spectral averaging, only 10% were significant (average F ratio, 3.9), but with time-domain averaging, 90% were significant (average F ratio, 19.3).

Table 1 also shows the average times for the responses to reach $P < 0.01$ by using time-domain averaging. An ANOVA of these data showed significant effects of intensity ($F_{2,18} = 6.9$; $P < 0.01$) and rate ($F_{2,18} = 10.8$; $P < 0.001$). The time taken to record a significant response was shorter for higher intensity and shorter for 40 or 50 Hz compared with 32 or 80 Hz.

Figure 2 illustrates the effects of intensity and rate on the amplitudes of the ASSRs after 160 s of time-domain averaging. An ANOVA showed a main effect of stimulus intensity ($F_{2,18} = 11.8$; $P < 0.01$), with the amplitude increasing regularly with increasing intensity, and a main effect of stimulus rate ($F_{4,36} = 27.1$; $P < 0.001$), with the amplitude being largest at 40 Hz and smallest at 80 Hz. The phase delay was different for each of the stimulus rates and increased with decreasing stimulus intensity ($F_{2,18} = 10.9$; $P < 0.01$).

Figure 3 shows the recordings in one subject in several states, and Figure 4 shows the amplitudes of the 40-Hz responses in each of the 100-s recordings, expressed as a percentage of the amplitude in the initial waking condition. For the 40-Hz responses, we obtained recordings from nine subjects in Stage 1, Stage 2, or both. The 40-Hz response amplitudes were significantly different across the 3 stages of arousal ($F_{2,18} = 32.2$; $P < 0.001$): 643 ± 190 nV for initial awake, 467 ± 170 nV for drowsiness and sleep, and 548 ± 154 nV for the final awake. These results indicate both adaptation (initial versus final) and arousal (drowsiness versus final) effects. The 80-Hz responses also showed a significant effect for condition ($F_{2,18} = 9.7$; $P < 0.01$): initial amplitudes (182 ± 86 nV) were larger than those seen for the other 2 (drowsiness, 148 ± 75 nV; final, 158 ± 70 nV), which were not significantly different from each other. Accordingly, the 80-Hz response was affected by adaptation but not by sleep.

Large PAMRs were seen in two subjects during sustained lateral gaze, and small PAMRs were seen in three others. Figure 5 shows the ASSRs from the left mastoid and vertex in the subject with the largest PAMR. Significant PAMRs were recorded from the mastoid during drowsiness with roving eye movements, but not without.

Table 1. Time to Record Significant Responses ($P < 0.01$)

Intensity (dB pSPL)	Measurement	Analysis type	Stimulus rate (Hz) 32	40	50	64	80
90	Incidence (%) after 16 s	Spectral averaging	10	30	20	0	20
		Long-time spectra	40	70	70	50	60
		Time-domain averaging	30	70	80	40	60
90	Time to reach significance (s)	Time-domain averaging	53 (2–246)	22 (2–92)	7 (2–26)	36 (2–168)	21 (4–44)
75	Incidence (%) after 16 s	Spectral averaging	0	20	40	0	0
		Long-time spectra	60	60	80	20	60
		Time-domain averaging	60	60	80	10	40
75	Time to reach significance (s)	Time-domain averaging	32 (4–150)	18 (2–56)	6 (2–26)	37 (6–132)	57 (10–146)
60	Incidence (%) after 16 s	Spectral averaging	0	20	10	0	0
		Long-time spectra	20	70	60	30	10
		Time-domain averaging	20	70	60	30	20
60	Time to reach significance (s)	Time-domain averaging	119 (8–658)	12 (2–40)	12 (2–28)	147 (2–1180)	103 (8–313)

At each intensity, the first three rows show the percentage of responses reaching a significance level of $P < 0.01$ after 16 s. The fourth row shows the average time taken (in seconds) to reach significance with time-domain averaging. The numbers in brackets represent the range in times (times >160 s were estimated).
pSPL = peak sound pressure level.

Discussion

Sensory evoked potentials recorded from the human scalp must be distinguished from EEG "noise." This noise may be generated in the brain, skin, eyes, and tongue and the muscles of the scalp, face, and neck. If the analysis is time-locked to the stimulus and if the noise is random relative to the stimulus, time domain averaging reduces the amplitude of the noise by the square root of the number of recordings averaged.

ASSRs are optimally evaluated in the frequency domain, where they are recognized as peaks at the rate of stimulation and its harmonics. To increase the SNR, the evoked potentials may be averaged in the time domain and then converted to the frequency domain. Similar results can be obtained by averaging in the frequency domain, but only if both amplitude and phase are considered—coherent averaging (18). Another approach is to base the frequency transform on a longer time period (18).

Pockett and Tan (7) used spectral averaging and did not consider phase. They essentially compared the response to the average amplitude of the noise recorded in two seconds. That they were still able to recognize significant responses in many subjects actually demonstrates how easy it is to record ASSRs after only two seconds. After analyzing 16 seconds of EEG, we obtained more than 4 times as many significant responses with time domain averaging or long-time spectra compared with spectral averaging (Table 1).

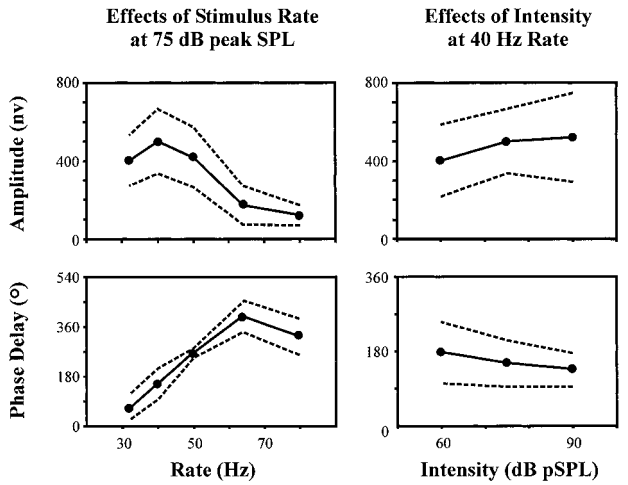

Figure 2. Effects of rate and intensity on the auditory steady-state responses (ASSRs). The left half of the figure shows the mean amplitudes and phases of the ASSRs across different stimulus rates. The right half of the figure shows the mean amplitudes and phases of the 40-Hz ASSR. The dashed lines show ±1 SD from the mean. The amplitude at 40 Hz was slightly larger than at 50 Hz, even though the average time to record the response as significant at 40 Hz was longer (Table 1). The longer average time was likely due to particularly noisy recordings at 40 Hz in 2 subjects. The means and SD for the phases were calculated with circular statistics. The slope of the phase versus rate data between 32 and 64 Hz gives an apparent latency of 29 ms. The discontinuity in phase between 64 and 80 Hz may in part be related to the 100-Hz low-pass filter. However, it also suggests that the 80-Hz response derives from a different generator than the other responses. pSPL = peak sound pressure level.

This is compatible with the extensive literature demonstrating that 40-Hz ASSRs can be rapidly and reliably recorded in waking adults (19).

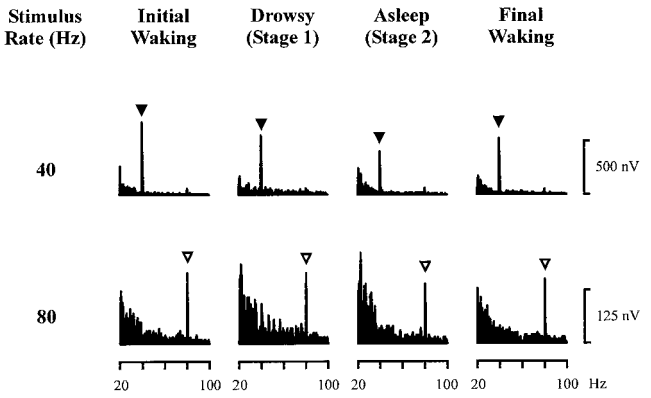

Figure 3. Effects of drowsiness and sleep in one subject. The spectra of the 40-Hz and 80-Hz auditory steady-state responses (ASSRs) are shown between 20 and 100 Hz for a single subject at different stages of arousal. The spectra were derived from the time-domain-averaged responses from 200 s of recordings (vertex-neck). The 80-Hz responses were plotted at a scale that was 4 times greater than the 40-Hz responses so that the changes related to arousal could be compared across both response types. For this particular subject, the 40-Hz response (▼) decreased to approximately 60% of its original amplitude during sleep and then increased in amplitude when the subject was woken up. The 80-Hz response (▽) decreased much less (to approximately 85%), and this decrease was likely related to adaptation because it persisted when the subject was woken up.

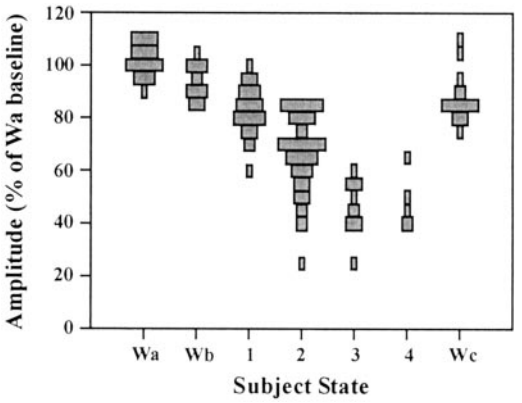

Figure 4. Effect of drowsiness and sleep on the amplitude of the 40-Hz auditory steady-state response (ASSR). This figure graphs the amplitudes of the 40-Hz ASSRs for each 100-s recording (all showing significant responses at $P < 0.01$). Not all subjects were recorded in each state of arousal, and only a few subjects went into Stage 3 or 4 sleep. For each subject, the amplitudes are expressed as a percentage of the mean amplitude in the initial waking condition. The results are plotted as histograms, with the width of the rectangle showing the number of recordings within each 5% range. The narrowest rectangle in the graph represents one recording in one subject. The Stage 1 recordings contain 25 data points (varying from 1 to 7 from each subject) from 7 subjects. The Stage 2 recordings contain 44 data points from 9 subjects (varying from 2 to 10 from each subject). Three different recordings occurred during wakefulness: Wa are the initial recordings with the eyes open, Wb are recordings with the eyes shut but no evidence of drowsiness, and Wc are the final recordings with the eyes open, taken after the subject was woken up. The amplitude of the response decreased during drowsiness (Stage 1) and sleep (Stages 2–4) and then returned toward the original values when the subject awakened (Wc).

Another possible problem when using the discrete Fourier transform is "scalloping," which attenuates activity between the discrete frequencies resolved by the analysis. With an epoch of two seconds and a frequency resolution of 0.5 Hz, ASSRs to stimuli presented at 40.25 rather than 40.00 Hz will be attenuated. In the first experiment, we used the same clock to control both the stimulus and the EEG digitization. This is not absolutely necessary (and we used separate clocks in the second experiment), but the problems of different clocks drifting out of synchronization must always be considered.

Although the SNR is a reasonable way to determine whether a recorded response is present, it is not the proper way to measure response amplitude. When one falls asleep, the 40-Hz response decreases in amplitude, but because the background EEG noise may also decrease (because of muscle relaxation), the SNR may not change much (8,9).

When using ASSRs to monitor anesthesia in the operating room, the optimal rates of stimulus presentation are 40 or 50 Hz, and the intensity should be 75- to 90-dB pSPL (Fig. 2). The term "40-Hz response" is a generic term for responses recorded by using stimuli at rates between 30 and 50 Hz. Within this frequency range, the amplitude and SNR of the response vary with the stimulus and the subject. In the first experiment, we found the amplitude largest at 40 Hz but the SNR largest at 50 Hz. 40-Hz responses should be recognized in most awake subjects within 16 seconds and in all subjects within 92 seconds (Table 1). Everyone showed significant responses within 64 seconds if we used a $P < 0.05$ level of significance. In the operating room, our experience is that recording between 30 and 60 seconds is almost always adequate to demonstrate a reliable 40-Hz response in a conscious subject.

Our results confirm that the 40-Hz responses, but not the 80-Hz responses, are reduced during sleep (8–10). During anesthesia with many different drugs, the 40-Hz responses are reduced much further than during sleep (1–5). Ketamine, however, does not decrease the amplitude of the 40-Hz response (20), suggesting that it causes unconsciousness via a different mechanism from other anesthetics.

The ASSR changes with drowsiness reported by Pockett and Tan (7) are not the same as those in the literature. Part of the discrepancy might relate to muscle noise during arousal, which increased the background noise and decreased the SNR (shown clearly in their Figure 2). However, Pockett and Tan also reported that some subjects showed an increased amplitude of the evoked potential during drowsiness. Their Figure 3 indicates a PAMR superimposed on the cerebral response during drowsiness. The PAMR is recorded from the mastoid with a peak negative wave at approximately 15 ms (equivalent to the peak positive wave in the vertex-mastoid montage of Pockett

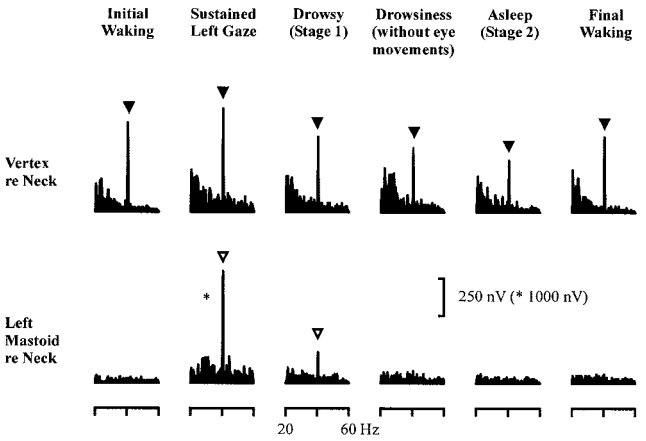

Figure 5. Postauricular muscle reflexes (PAMRs). This figure shows the 40-Hz auditory steady-state response (ASSR) recorded from the vertex and left mastoid by using a neck reference. The response at the vertex (▼) gets smaller with drowsiness and sleep and then increases in amplitude when the subject is woken up. The response at the left mastoid (▽) is particularly large during sustained leftward gaze, where it reaches amplitudes of approximately 3 μV. The scale is decreased (*) for this particular recording condition and electrode site because of the very large PAMR. There was also some PAMR activity during drowsiness. This did not occur if we restricted the analysis to periods of drowsiness wherein there were no rolling-eye movements (fourth column).

and Tan) (11–13). Moving the reference from the mastoid to the neck eliminates the PAMR. Our recordings from one subject with a large PAMR (Fig. 5) indicate that the PAMR may be enhanced during drowsiness because of the large rolling-eye movements. Depending on its phase, this mastoid PAMR could enhance the amplitude of the 40-Hz ASSR recorded between vertex and mastoid. This would not occur with a neck reference or during anesthesia, when the PAMR would be attenuated by the anesthetic or the neuromuscular blockade. Muscles of the neck can be reflexly activated (the "inion reflex"), but only with very loud sounds and only when the muscles are actively contracting (21).

The rationale for using the 40-Hz ASSR to monitor the effects of general anesthetics on consciousness is based on 2 premises. First, endogenous thalamocortical γ rhythms are likely necessary for consciousness (22). Second, the 40-Hz ASSR and the endogenous γ rhythms probably share the same thalamocortical generators. The robust association between attenuation of ASSR and unconsciousness caused by conventional general anesthetics suggests that anesthetic-induced unconsciousness is associated with a reduction of 40-Hz activity in thalamocortical systems and provides a reasonable basis for using the 40-Hz ASSR to monitor anesthesia.

Consciousness and awareness are multidimensional phenomena, which cannot be fully assessed with a single physiological measurement. Nevertheless, the problem of inadvertent intraoperative awareness is important, particularly during pharmacological blockade of neuromuscular or autonomic reactivity (23). The 40-Hz ASSR, when recorded with an amplitude similar to that when the patient is demonstrably conscious, indicates that the cortex is in a state compatible with awareness. As such, we believe that it remains a useful measurement during anesthesia. The relative effectiveness of monitoring the anesthetic state through specific effects of sensory stimulation (e.g., ASSR) or more general EEG measurements of the brain state remains to be determined (24,25).

The authors thank James Knowles, the Catherall Foundation, and the Baycrest Foundation for their support. Patricia Van Roon performed the recordings and assisted with the analysis of the data. Chenghua Wang and Ali Mazaheri helped with the programming. MSJ and TWP have licensed some of the MASTER technology for hearing assessment to Biologic Systems Corporation.

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