UC Irvine

UC Irvine Previously Published Works

Title

Intensity changes in a continuous tone: auditory cortical potentials comparison with frequency changes.

Permalink

<https://escholarship.org/uc/item/12b934f3>

Journal

Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 120(2)

ISSN

1388-2457

Authors

Dimitrijevic, Andrew
Lolli, Brenda
Michalewski, Henry J
et al.

Publication Date

2009-02-01

DOI

10.1016/j.clinph.2008.11.009

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, availalbe at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Intensity changes in a continuous tone: Auditory cortical potentials comparison with frequency changes

Andrew Dimitrijevic *, Brenda Lolli, Henry J. Michalewski, Hillel Pratt, Fan-Gang Zeng, Arnold Starr

Department of Neurology, University of California, 150 Med Surge 1, Irvine, CA 92697, USA

ARTICLE INFO

Article history:

Accepted 9 November 2008

Available online 27 December 2008

Keywords:

N100
Intensity change
Dipole source analysis
Evoked potentials
Auditory

ABSTRACT

Objectives: To examine auditory cortical potentials in normal-hearing subjects to intensity increments in a continuous pure tone at low, mid, and high frequency.

Methods: Electrical scalp potentials were recorded in response to randomly occurring 100 ms intensity increments of continuous 250, 1000, and 4000 Hz tones every 1.4 s. The magnitude of intensity change varied between 0, 2, 4, 6, and 8 dB above the 80 dB SPL continuous tone.

Results: Potentials included N100, P200, and a slow negative (SN) wave. N100 latencies were delayed whereas amplitudes were not affected for 250 Hz compared to 1000 and 4000 Hz. Functions relating the magnitude of the intensity change and N100 latency/amplitude did not differ in their slope among the three frequencies. No consistent relationship between intensity increment and SN was observed. Cortical dipole sources for N100 did not differ in location or orientation between the three frequencies.

Conclusions: The relationship between intensity increments and N100 latency/amplitude did not differ between tonal frequencies. A cortical tonotopic arrangement was not observed for intensity increments. Our results are in contrast to prior studies of brain activities to brief frequency changes showing cortical tonotopic organization.

Significance: These results suggest that intensity and frequency discrimination employ distinct central processes.

© 2008 International Federation of Clinical Neurophysiology. Published by Elsevier Ireland Ltd. All rights reserved.

1. Introduction

The purpose of this study was to examine cortical potentials associated with brief intensity changes and to contrast these results with our prior study examining cortical potentials to brief frequency changes (Dimitrijevic et al., 2008). We chose to study brief intensity and frequency changes because everyday sounds such as speech and music contain these types of elements. Event related potential (ERP) studies have typically used tone burst stimuli that contain at least two features: intensity change and frequency change. The goal of this paper and the companion paper (Dimitrijevic et al., 2008) was to vary only one stimulus attribute, e.g., intensity (this study) or frequency (previous study) in otherwise continuous tones.

There have been a limited number of studies examining brain activity accompanying changes in frequency or intensity. The general finding was that N100/P200 potentials could be elicited. Spoer et al. (1971) showed that N100 amplitudes were larger for intensity changes of continuous stimuli compared to tone bursts. Both Jerger and Jerger (1971) and Harris et al. (2007) showed a signifi-

cant relationship between N100/P200 amplitude and the magnitude of intensity change. Harris et al. (2007) used both 500 and 3000 Hz as stimuli with young and elderly normal hearing adults. The young control group showed no differences between N100/P200 across the two frequencies whereas the older group showed a frequency effect such that N100 responses were larger and later to low than high frequencies. The authors attributed this difference to an age-related reduction in temporal processing and not to changes of audibility.

There have been several behavioral studies comparing intensity discrimination for continuous versus interrupted stimuli (Carlyon and Moore, 1986; Turner et al., 1989; Bacon and Viemeister, 1994; Moore et al., 1997). These studies have shown that thresholds are lower for continuous stimuli compared to transient or “gated” stimuli. One possible reason for this difference may be related to the fact that the subject is performing a “change” detection strategy rather than relying on the memory of previous intensity transients (Durlach and Braida, 1969).

In the present experiment we examined cortical potential changes as a function of both frequency and the magnitude of intensity increments. Our previous work (Dimitrijevic et al., 2008) showed that there were differences in the slope functions (N100 latency versus magnitude of frequency change) between

* Corresponding author. Tel.: +1 949 824 7605; fax: +1 949 824 2132.
E-mail address: adimitri@uci.edu (A. Dimitrijevic).

low and high frequencies, with low frequency (250 Hz) showing a steeper slope than the high frequency (4000 Hz). This difference may be related to longer temporal integration times for low versus high frequencies. We hypothesized that similar to our previous study, cortical latency and amplitude differences would exist between high and low frequencies for the encoding of intensity increments.

2. Methods

2.1. Subjects

Twelve (6 males) subjects (mean age: 24 years, 11 self-reported right-handed) with pure tone thresholds below 25 dB HL (500–6000 Hz) with no history of neurological deficits participated in the study after giving written informed consent.

2.2. Stimuli

Stimuli were continuous tones of 15 min duration containing brief intensity changes lasting 100 ms occurring every 1.4 s and presented at an 80 dB SPL baseline level. The frequencies were 250, 1000, and 4000 Hz and the magnitude of intensity changes were 0, 2, 4, 6, and 8 dB. The onset and offset of the intensity increment was windowed using 5 ms Blackman window. A schematic illustration of an intensity change is shown in Fig. 1. This change envelope is in contrast to the onset and offsets of frequency change of our companion study which were instantaneous without accompanying changes of signal amplitude. The order of each of the intensity increases was randomized as well the presentation of 250, 1000, and 4000 Hz tones.

2.3. Recordings

A 64-channel Neuroscan Synamps² recording system was used to collect electrophysiological data. The electrode placements were very similar to the 10% system (Nuwer et al., 1998) except that electrodes NZ, AF3, and AF4 were not included and replaced by two other electrodes at an intermediate distance between PO7 and O1 (CB1), and between PO8 and O2 (CB2). Electrode impedances were kept below 10 k Ω . Vertical electro-oculograms (EOGs) were recorded using two bipolar electrodes above and below the right eye and horizontal EOGs were recorded using two bipolar electrodes on left and right outer canthi. Signals were amplified, digitized at 1000 Hz, and bandpass filtered (0.05 and 40 Hz). Trials were extracted using a –200 to 1900 ms window. Offline analysis included re-referencing the recordings to an average reference (excluding the EOGs). Eye blink correction was performed in each

subject using a singular value decomposition-based spatial filter based on principal component analysis of averaged eye blinks for each subject (Ille et al., 2002). Averages for each of the intensity changes were based on 100 trials.

2.4. Procedures

Subjects were seated in a comfortable reclining chair and watched a silent, closed-captioned movie of their choice. Stimuli were presented monaurally to either the left or right ear and the associated electroencephalogram was recorded. In order to avoid fatigue, subjects were given the option of rest periods every 15 min. Additionally, the ongoing EEG was continuously monitored for excessive theta activity which might indicate decreased vigilance.

2.5. Psychoacoustic measures

Subjects were asked to respond by button press when they heard the continuous tone become momentarily louder. The stimuli were identical to what was used during the passive condition. Although we recorded the brain potentials during this “active” task, only the data from the passive condition are presented here. Performance versus intensity change functions were plotted for both detection and reaction time for each intensity increment. Because of time constraints, not all subjects performed the psychoacoustic measurements for each frequency. The corresponding number of subjects that participated in the active condition was as follows: 250 Hz – 10 subjects; 1000 Hz – 6 subjects; and 4000 Hz – 6 subjects.

2.6. Waveform analysis

After low-pass filtering (40 Hz) and baseline correcting (200 ms) peak analysis was carried out for the FCz electrode since it always had the largest N100. N100 peaks were defined as the most negative peak in the 70–150 ms post stimulus range. Peak measurements of P200 were not examined as because not all subjects showed a clear peak.

2.7. Dipole source analysis

Dipole source analysis was performed using Neuroscan's Source software. In order to improve the signal to noise ratio, the responses to the 6 and 8 dB intensity changes were averaged together for each subject separately for each frequency. Dipole modeling was performed on the individual averaged waveforms after bandpass filtering (1–30 Hz, 12 dB/octave). A fixed two dipole model was symmetrically applied using a three-shell spherical head model using the same three-dimensional channel coordinates for each subject. Consequently, the precise individual source locations for each subject were not known because they were based on an averaged head shape. The source activity was allowed to vary in location, orientation, and strength and was applied to a ± 20 ms window around the N100 peak as measured by the peak in global field power. A criterion of 90% goodness of fit (GOF) or better was used to determine if a fit was significant in each subject. A second grand average was performed using only those subjects who had GOFs above 90%. The number of subjects having GOFs above 90% were 7 (for 250 Hz), 8 (for 1000 Hz), and 10 (for 4000 Hz). Separate grand averages based on these subjects were made and then the dipole source analysis was repeated.

Dipole locations (NeuroScan Source native format) are given in (x, y, z) coordinates measured in millimeters where x extends left to right (negative to positive) where 0 is in the middle. y extends anterior to posterior (positive to negative) where 0 is in the middle.

Fig. 1. Schematic illustration of the stimulus showing two consecutive intensity increments lasting 100 ms and separated by 1.4 s.

z extends superior to inferior where 0 is at the base of the bottom of the brain at the same plane as the bottom of the cerebellum.

2.8. Statistical analysis

Repeated measures ANOVAs were used to examine the effects of intensity change on N100 amplitude and latency and slow negativity (SN) amplitude. Two types of ANOVAs were performed: (1) one-way: effects of Δ dB for each of the frequencies separately and (2) two-way ANOVA [Δ dB $\times$ frequency] was performed to directly compare the effect of frequency. Separate ANOVA's were performed because there was an uneven number of significant N100s across frequencies and Δ dB. Accordingly, the 250 Hz data was analyzed for 4, 6, and 8 dB increments and 2, 4, 6, and 8 dB increments for the 1000 and 4000 Hz data. The comparisons across frequencies were based on 4, 6, and 8 Δ dB. Post-hoc comparisons were made using the Tukey Honestly Significant Difference test.

The relationship between the magnitude of the intensity increment and N100 was analyzed by plotting the magnitude of intensity change (abscissa) and N100 latency/amplitude (ordinate) and examining both the slope and Pearson correlations of each function. Differences between slopes were tested using an ANCOVA (Zar, 1999).

The identification of the SN was quantified as follows: the standard deviation of each subject's prestimulus baseline (200 ms) was calculated. Next the amplitude of the SN was quantified by taking the average amplitude from 300 to 600 ms. If the SN amplitude exceeded two standard deviations from baseline then the response was scored as having a significant SN. This was repeated for each intensity change and subject. These evaluations of the SNs differed from our previous study. Here, the data are collapsed across all subjects and intensity increments that were significant were observed. This is different from the previous study that only included subjects who presented significance at all frequency changes. If we had chosen to use the same criteria for inclusion, the sample size would have been too small for statistical analyses (2, 3, and 3 for 250, 1000, and 4000 Hz respectively).

Differences in dipole orientation between hemisphere (left versus right dipole in all three planes) and differences between 250, 1000, and 4000 Hz (each plane and hemisphere separately analyzed) were assessed using the Watson–Williams test (Zar, 1999, pp. 625). This test is designed to evaluate differences between 2 or more groups of vectors and takes the form:

$$F = K \times (N - 2)(R_1 + R_2 - R)/(N - R_1 - R_2),$$

where K is a correction factor related to the bias in the F calculation; N is the combined sample size (groups 1 and 2); R_1 and R_2 are Rayleigh values for each group; and R is a weighted average of the R_1 and R_2 . Individual subjects (pooled across 8 and 6 Δ dB) were used in this statistic.

Differences in dipole location were assessed using a repeated measures ANOVA comparing 250, 1000, and 4000 Hz.

3. Results

3.1. Psychoacoustic measures (accuracy and reaction times)

There were significant differences in the behavioral detection of intensity changes for low and middle/high frequencies. Subjects detected nearly 100% of intensity changes of 4, 6, and 8 dB for 1000 and 4000 Hz frequencies but not for 250 Hz. A repeated measures ANOVA tests demonstrated a significant interaction between the frequencies and intensity change [$F(6,24) = 16.2$; $P < 0.001$]. Post-hoc testing showed that the 250 Hz 2 dB increment detection was less than 1000 and 4000 Hz ($P < 0.001$) and similarly for the 4 dB increments compared to 1000 ($P = 0.005$) and 4000 Hz ($P < 0.007$). A main effect of frequency on reaction times was observed [$F(2,8) = 27.4$; $P < 0.001$]. Post-hoc analysis showed that 250 Hz reaction times were longer than both 1000 Hz ($P = 0.003$) and 4000 Hz ($P = 0.0006$). No differences were seen between 1000 and 4000 Hz. Fig. 2 shows the plots of detection and reaction times for 250 Hz (circle), 1000 Hz (square), and 4000 Hz (triangle).

3.2. Cortical potentials

Fig. 3 illustrates intensity increases of 8 dB (schematically shown at the top) for three tones and the accompanying grand mean potentials (FCz). The N100, P200, and the SN are identified. The N100 peak was earlier for 4000 and 1000 Hz compared to 250 Hz. Unlike the previous study using frequency change P200 was not consistently observed. The response here was mainly dominated by an N100 with a return to baseline.

Fig. 4 (left column) shows the grand mean averaged waveforms for all the intensity increments and frequencies. All subjects had an N100 for the 8 dB change for 1000 and 4000 Hz frequencies whereas ten out of twelve subjects had an N100 to the 250 Hz frequency (Table 1).

The SNs obtained in the current study differed from our companion study of frequency change in that it was not consistently identified for all subjects and conditions. The grand average plots

Fig. 2. Mean and standard errors of the behavioral measures showing the detection (left panel) and reaction times (right panel). * Significant post-hoc differences between 250 and 1000/4000 Hz; ** significant main effect of 250 Hz.

Fig. 3. Relationship between stimulus and evoked potentials. The stimulus was a continuous pure tone with periodic changes in intensity lasting 100 ms (top). An 8 dB change is shown. Below are grand averaged potentials to the intensity change for frequencies of 250, 1000, and 4000 Hz stimuli. The potentials include an N100, P200, and slow negativity.

in Fig. 4 show the SN (300–600 ms) as a function of the magnitude of intensity increment. Although present in the grand average (and in Table 1), the SN for individual subjects did not show an orderly relationship with the magnitude of intensity increase. This is in contrast to our earlier study, where most subjects who had an SN at the largest frequency change also had SNs at smaller frequency changes. Only two subjects (out of 12) for 250 Hz had SNs at all 8, 6, and 4 dB increments. Similarly, only three subjects (out of 12) had SNs for 1000 and 4000 Hz. The other subjects had SNs but did not show an orderly pattern (e.g. significant at 2, 6, and 8 dB, but not at 4 dB; Table 1). The likelihood of finding SN as a function of tone frequency and magnitude of intensity change is shown in Table 1 and is greater for 6 and 8 dB than for 4 and

Table 1

Proportion of subjects (out 12) showing a significant N100 or SN.

	Δ dB				
	8	6	4	2	0
N100					
250 Hz	0.83	0.83	0.75	0.50	–
1000 Hz	1.00	0.92	0.83	0.67	–
4000 Hz	1.00	1.00	1.00	0.58	–
SN					
250 Hz	0.50	0.42	0.50	0.25	0.25
1000 Hz	0.50	0.58	0.50	0.50	0.08
4000 Hz	0.75	0.42	0.58	0.42	0.25

2 dB. There were no significant trends found between intensity change and the incidence and amplitude of the SN.

3.3. N100 and intensity change

Similar to our previous study of frequency increases, N100 amplitude was larger and latency was earlier with increasing magnitudes of change (Fig. 4). Mean N100 amplitude and latencies for intensity change are plotted in Fig. 5 and are shown in Table 2.

3.3.1. Latency

A repeated measures ANOVA for 250 Hz latency showed a main effect of intensity where larger intensity increments resulted in earlier N100 peaks [$F(2,14) = 7.33$; $P = 0.007$]. Post-hoc analysis showed no difference between 8 and 6 dB increments but the 8 dB increment was significantly earlier than the 4 dB increment ($P = 0.002$). Similarly, a main effect of intensity increment was seen with 1000 Hz [$F(3,18) = 4.30$; $P = 0.019$] and post-hoc analysis showed 8 and 6 dB increments yielded earlier N100's compared to 2 dB, ($P = 0.012$ and $P = 0.019$, respectively). With the 4000 Hz frequency, a main effect of intensity increment was observed [$F(3,15) = 4.48$; $P = .020$]. Post-hoc analysis did not show significant latency differences between the intensity increments.

3.3.2. Amplitude

A repeated measures ANOVA for 250 Hz showed a main effect of intensity for N100 amplitudes [$F(2,14) = 11.66$; $P = 0.001$]. Post-hoc analysis showed that the 8 dB intensity increment was larger than both 6 dB ($P = 0.021$) and 4 dB ($P < 0.001$). Similarly, the 1000 Hz showed a main effect of intensity [$F(3,18) = 5.48$;

Fig. 4. Grand mean evoked potentials to all the intensity changes from frequencies of 250, 1000, and 4000 Hz.

Fig. 5. Mean and standard errors of N100 amplitude and latency as functions of intensity change magnitude. Note that there are no differences in the slopes across all three frequencies.

$P = 0.004$] and post-hoc analysis revealed that the 2 dB increment was smaller than 8 dB ($P < 0.001$) and 6 dB increments ($P = 0.015$). The 4000 Hz frequency also showed a main effect of intensity [$F(3, 15) = 12.55$; $P < 0.001$]. Post-hoc analysis demonstrated that the 2 dB increment was smaller than the 8 dB ($P < 0.001$) and 6 dB ($P < 0.001$). Additionally, the 4 dB increment was smaller than the 8 dB ($P = 0.004$). No significant differences were seen with ear of stimulation.

3.3.3. Frequency comparisons

The N100 amplitude did not differ between the three frequencies. However, main effects of frequency were indicated on N100 latency [$F(2, 14) = 6.1$; $P = 0.012$]. Post-hoc analysis revealed that the 250 Hz latency was later than both the 1000 Hz ($P = 0.007$) and 4000 Hz ($P = 0.008$).

3.4. N100 correlations with magnitude of intensity change

Significant correlations were observed between intensity change magnitude and N100 amplitude for all three frequencies (Fig. 5). In contrast to our previous study of frequency change (Dimitrijevic et al., 2008), no significant slope differences (Δ dB versus N100 latency/amplitude) were observed between the three frequencies for latency [$F(2, 78) = 0.15$; $P = 0.860$] and amplitude [$F(2, 78) = 0.33$; $P = 0.718$].

3.5. Slow negativity and intensity change

Fig. 6 illustrates the SN amplitude as a function of intensity increment. There was a significant correlation between intensity increment and SN for 250 but not 1000 and 4000 Hz. This result is similar to the effects of frequency change for 250 and 4000 Hz of our prior study.

3.6. Dipole source analysis

Dipole amplitudes were approximately 20% larger on the contralateral side for all frequencies but this difference was not significant. Data from left and right ears were therefore pooled. The grand averaged dipole fits based on these subjects are shown in Fig. 7 and a comparison of the locations is shown in Fig. 8.

Subject means and standard deviations of dipole strengths, location, orientation and GOFs are shown in Table 3. No significant differences were seen in any of the orientations between 250, 1000, and 4000 Hz. Although the 4000 Hz dipole tended to be more posterior than the 250 and 1000 Hz, this shift was not significant. No differences in dipole magnitude were seen across 250, 1000, and 4000 Hz.

4. Discussion

Auditory cortical potential latencies and amplitudes accompanying increases of intensity of continuous tones (250, 1000, or 4000 Hz) did not differ as a function of the frequency of the tones. These findings differ from our previous study (Dimitrijevic et al., 2008)¹ showing that latencies and amplitudes of auditory cortical N100 potentials accompanying frequency changes in continuous tones differ between high- and low-base frequency of the tones. The results from the two studies will be discussed in relation to central and peripheral auditory processes encoding intensity and frequency changes.

4.1. Changes of intensity

There have been several studies of brain activity accompanying changes of intensity of continuous tones showing that the amplitude of cortical N100 potentials increases with the magnitude of the intensity increment (Harris et al., 2007; Makela et al., 1987; Jerger and Jerger, 1971; McCandless and Rose, 1970; Martin and Boothroyd, 2000). Harris and colleagues (2007) compared cortical potentials to intensity increments for low (500 Hz) and high frequency (3000 Hz) tones and did not show significant differences.

These findings appear to be consistent with some of the descriptions of auditory nerve activity accompanying changes of intensity that were generally independent of the frequency of the tones (Rose et al., 1971; Heil and Neubauer, 2001). High spontaneous rate nerve fibers generally have lower thresholds and exhibit firing rate saturation at low stimulus intensities. These fibers's discharge rate functions would likely have saturated by 80 dB SPL, the stim-

¹ A different group of young normal-hearing subjects were used. Because these subjects were all normal hearing, of similar ages and similarly divided by gender, comparison between the two studies was deemed justified.

Table 2

Mean N100 amplitude and latency.

Δ dB	N100 amplitude (mean μ V $\pm$ SD)			N100 latency (mean ms $\pm$ SD)			SN amplitude (mean μ V $\pm$ SD)		
	250 Hz	1000 Hz	4000 Hz	250 Hz	1000 Hz	4000 Hz	250 Hz	1000 Hz	4000 Hz
8	−3.5(0.3)	−3.8(0.5)	−3.3(0.4)	132(4)	118(3)	114(3)	−1.3(0.3)	−1.0(0.5)	−1.1(0.5)
6	−2.5(0.3)	−3.3(0.5)	−2.4(0.5)	141(4)	121(3)	124(6)	−0.8(0.3)	−1.0(0.6)	−0.9(0.6)
4	−2.1(0.3)	−3.1(0.3)	−2.5(0.3)	147(6)	124(3)	127(9)	−0.9(0.2)	−1.1(0.6)	−1.0(0.8)
2	−1.4(0.2)	−1.9(0.1)	−2.4(0.3)	156(14)	139(8)	135(18)	−0.6(0.3)	−0.9(0.5)	−1.2(0.5)

ulus level used in our experiment. The low spontaneous rate fibers show relatively higher thresholds and appear to be of two subtypes: saturating and non-saturating (Winter and Palmer, 1991). It is most likely that with intensity increments the non-saturating nerve fibers would be progressively activated with intensity increments and could account for increases of N100 at the intensities used in the present study.

Fig. 9a summarizes the amplitude and latency of N100 to changes of intensity (left) while the right side schematically represents auditory nerve single unit response properties (based on Rose et al., 1971) for both 250 and 4000 Hz accompanying changes of intensity. Note that both the numbers of units and their rate or synchrony of discharge increase relatively equivalently for low and high frequency tones, consistent with the finding that N100 amplitudes for intensity changes of low and high frequencies were not significantly different.

N100 latency in this and other studies (Jacobson et al., 1992; Woods et al., 1993; Stufflebeam et al., 1998) have shown the measure to be longer by approximately 20 ms to tones of low than high frequencies (Jacobson et al., 1992). Moreover, the differences in latency for low and high frequencies were maintained in the present study when intensity was increased. These latency differences can be only partially accounted for by the 4 ms difference of travel time of excitation for low and high frequencies along the cochlear partition (Don and Eggermont, 1978). The major share of the difference reflects distinct central processes acting for low and high frequency tones.

Most of the previous studies examining N100 and intensity have used tone bursts presented in a quiet background. The general finding in these studies (Naatanen and Picton, 1987) is that N100 amplitude increases and latency decreases with increasing intensity with their functions saturating close to 100 dB SPL. It is difficult to relate the present results with the previous studies as we inserted changes of intensity in a continuous ongoing stimulus. The changes of N100 latency in the present study is consistent with animal data showing intensity changes affect auditory nerve activ-

ity in similar manner across frequency and rise times for a range of intensities (Heil and Neubauer, 2001). Auditory nerve activity appeared to be related to sound “pressure integration” where the area of a sound onset versus time function predicted the increase of nerve activity. For the stimuli used in the present study the rate of sound pressure increase (or acceleration) is greatest with the 8 dB increments and lowest with the 2 dB increments consistent with the shortening of latency as intensity increased accounting for shorter N100 latencies with greater intensity increments.

4.2. N100 dipole generators accompanying intensity change

The dipole location or orientation of N100 in the present study were not different for intensity changes of 250, 1000, and 4000 Hz tones. This result is unexpected since a tonotopic arrangement showing medial to lateral for high to low frequencies has been well appreciated for the auditory N100 (Pantev et al., 1995). A medio-lateral shift of N100 dipoles was observed in our previous study accompanying frequency changes (Dimitrijevic et al., 2008). The conclusion that intensity increments activate similar areas of cortex regardless of the frequency is consistent with experimental animal studies showing that at high stimulus intensities (80 dB SPL) the tonotopic arrangement is no longer apparent (Phillips et al., 1994).

The dipole analysis in the present study did show a trend towards more superficial (lateral) sources for greater intensity increments compared to lower intensity increments. This type of “ampliotopic” coding has been previously described using magneto-encephalography (Pantev et al., 1989) and fMRI (Bilecen et al., 2002) for a 1000 Hz tone.

4.3. Comparisons with N100 measures accompanying changes of frequency

As described above, the peripheral auditory nerve model accompanying intensity changes in Fig. 9a corresponds to the N100 results for latency, amplitude but not for cortical dipole localization. We now address cortical N100 latency, amplitude, and dipole localization accompanying frequency change to define similarities and differences from the intensity changes.

Both the “place” of origin of nerve fiber along the cochlea partition (von Békésy, 1960) as well as the temporal pattern or synchrony (Rose et al., 1967) of discharge define the response properties (tuning curves) for units. High and low frequency units discharge patterns are used in Fig. 9 based on studies of monkey auditory nerve (Rose et al., 1971). Note that for both low and high frequency tones a 50% change in frequency shifts the point of maximum discharge towards the new upper frequency (Fig. 9b). With the shift of high frequencies, a new population of fibers centered at 6000 Hz was activated, overlapping with some of the former population responsive to 4000 Hz. It is likely that the number of neural elements responding to 4000 and 6000 Hz tones are approximately equal. In contrast, for low frequencies (e.g., 250 Hz), an equivalent 50% shift to 375 Hz activates both a new population of units as well as maintaining the temporal response

Fig. 6. Mean and standard errors of the slow negativity (SN) for all three frequencies.

Fig. 7. N100 equivalent dipoles and intensity changes. All three frequencies are overlaid on a standard MRI image. Note similar orientations across frequencies.

to the original lower 250 Hz frequency. Thus the numbers of responsive units actually increase for changes of low frequency but not for high ones. These peripheral auditory coding mechanisms appear to account for both the stability of N100 amplitudes to changes of 4000 Hz tones (the numbers and rate of discharge of units remain constant) and for the increase of amplitudes to changes of 250 Hz tones (both the numbers of neurons involved and their temporal entrained responses increase). However, the latency decrease accompanying the pitch change of 250 Hz (Fig. 9, left column) cannot be accounted for by peripheral mechanisms. Therefore this suggests that the central auditory pathway requires longer processing times for low versus high frequencies.

From an ecological view point, change of frequency signals a new auditory object in the scene, or a marked change in an existing object such as the Doppler effect due to fast motion toward or away from the listener, or a meaningful communication or warning call (Neuhoff, 1998). In contrast, change of intensity without a change in frequency may signal a slower moving object or particular vocal features such as emphasis or affect in vocal communications. It is therefore not surprising that the two types of change are processed differently.

4.4. Relations to psychoacoustics

Although this study did not measure thresholds directly, there was a good agreement between physiological and behavioral measures. Half of the subjects had N100s to the 2 dB intensity increments for 250 Hz and more than half of the subjects had responses to the 2 dB change with 1000 and 4000 Hz. This relates well to the behavioral results of this study showing that detection was better for 1000 and 4000 Hz. It is difficult to relate our findings with psychoacoustic literature because the continuous tone paradigm is not typically used. Nonetheless our physiological and behavioral results are similar to previously published behavioral studies using gated (Jesteadt et al., 1977; Florentine et al., 1988; He et al., 1998) and continuous tonal stimuli (Moore et al., 1997; Turner et al., 1989). These studies have typically found intensity thresholds near 1 dB for frequencies ranging from 250 to 4000 Hz. Slight increases in threshold are seen at stimulus levels below 50 dB SPL and at frequencies at 8000 Hz and higher. Our results show that intensity increments at 250 Hz response was less detectable and had smaller evoked N100 responses compared to these same measures at 1000 and 4000 Hz similar to traditional

Fig. 8. Mean and standard errors of N100 dipole locations for 250, 1000, and 4000 Hz. The three orthogonal planes are shown in the three rows. Data are given on the left column. The box overlaying the brain shows the location and extent of the axis of the data on the left. Note that there are significant differences in location between the three frequencies.

psychoacoustic studies of intensity discrimination thresholds for high versus low frequencies.

4.5. Slow negativity

The SN we observed in this experiment was smaller and was elicited less frequently compared to our previous report using

frequency changes. Although more work is needed to characterize the SN, the clear differences between frequency and intensity change suggest that its nature is stimulus dependant. The SN may represent a sustained DC baseline shift arising from repeated stimulation. It is possible that with changes in frequency a larger portion of cortex is stimulated compared to intensity changes.

Table 3

Summary of dipole analysis mean (SD).

Frequency (Hz)	Hemisphere	Strength (nAm)	Location (mm)			Orientation (°)			Goodness of fit (%)
			x	y	z	z/x	z/y	y/x	
250	Left	35(9)	−41(9)	3(10)	66(7)	−119(29)	−49(19)	−119(23)	96(2)
250	Right	33(23)	41(9)	3(10)	66(7)	−67(36)	−51(32)	−76(47)	
1000	Left	32(15)	−42(7)	7(7)	66(5)	−105(21)	−49(8)	−106(22)	97(2)
1000	Right	35(17)	42(7)	7(7)	66(5)	−84(17)	−52(15)	−83(29)	
4000	Left	33(17)	−42(9)	0(10)	65(8)	−156(11)	−47(18)	−108(24)	96(3)
4000	Right	26(14)	42(9)	0(10)	65(8)	−144(29)	−65(25)	−46(46)

Fig. 9. (A) Intensity change: The left column summarizes N100 amplitude and latencies as a function of intensity increment. The right column shows the predicted auditory nerve activity when intensity is increased (dotted). (B) Frequency change: The left column summarizes N100 amplitude and latencies as a function of frequency increment. The right column shows the predicted auditory nerve activity when frequency is increased (dotted). Auditory nerve activity based on Rose et al. (1971).

4.6. P200

In contrast to our previous study where a P200 could be observed (often not reaching above baseline amplitude) the intensity change stimulus predominantly evoked an N100 followed by a return to baseline. The diminution of P200 might be related to the 100 ms duration of the intensity increase. The N100 offset occurs at the same time as the P200 onset. A linear addition between these two responses might explain why the P200 did not reach above baseline levels in the frequency change experiment. Because the P200 waveform morphology is so different across the two studies, it is also possible that the absence of the P200 is specifically related to intensity change stimuli.

In summary, these N100 data provide evidence that cortical processes accompanying brief intensity increments of a continuous tone are similar for low, medium, and high frequencies consistent with the patterns of auditory nerve activity to these stimuli. Using the same continuous stimulus paradigm for frequency changes, N100 latency measures were very different between high and low frequencies and reflected additional central auditory processing of the auditory nerve inputs. These observations strengthen the idea that central processing of intensity and of frequency cues differ as reflected by N100 latency and dipole localizations.

References

- Bacon SP, Viemeister NF. Intensity discrimination and increment detection at 16 kHz. *J Acoust Soc Am* 1994;95:2616–21.
- Bilecen D, Seifritz E, Scheffler K, Henning J, Schulte AC. Amplitude of the human auditory cortex: an fMRI study. *Neuroimage* 2002;17:710–8.
- Carlyon RP, Moore BC. Continuous versus gated pedestals and the “severe departure” from Weber’s law. *J Acoust Soc Am* 1986;79:453–60.

- Dimitrijevic A, Michalewski HJ, Zeng FG, Pratt H, Starr A. Frequency changes in a continuous tone: auditory cortical potentials. *Clin Neurophysiol* 2008;119:2111–24.
- Don M, Eggermont JJ. Analysis of the click-evoked brainstem potentials in man using high-pass noise masking. *J Acoust Soc Am* 1978;63:1084–92.
- Durlach NI, Braida LD. Intensity perception. I. Preliminary theory of intensity resolution. *J Acoust Soc Am* 1969;46:372–83.
- Florentine M, Fastl H, Buus S. Temporal integration in normal hearing, cochlear impairment, and impairment simulated by masking. *J Acoust Soc Am* 1988;84:195–203.
- Harris KC, Mills JH, Dubno JR. Electrophysiologic correlates of intensity discrimination in cortical evoked potentials of younger and older adults. *Hear Res* 2007;228:58–68.
- He N, Dubno JR, Mills JH. Frequency and intensity discrimination measured in a maximum-likelihood procedure from young and aged normal-hearing subjects. *J Acoust Soc Am* 1998;103:553–65.
- Heil P, Neubauer H. Temporal integration of sound pressure determines thresholds of auditory-nerve fibers. *J Neurosci* 2001;21:7404–15.
- Ille N, Berg P, Scherg M. Artifact correction of the ongoing EEG using spatial filters based on artifact and brain signal topographies. *J Clin Neurophysiol* 2002;19:113–24.
- Jacobson GP, Lombardi DM, Gibbens ND, Ahmad BK, Newman CW. The effects of stimulus frequency and recording site on the amplitude and latency of multichannel cortical auditory evoked potential (CAEP) component N1. *Ear Hear* 1992;13:300–6.
- Jerger J, Jerger S. Evoked response to intensity and frequency change. *Arch Otorhinolaryngol* 1971;91:433–6.
- Jesteadt W, Wier CC, Green DM. Intensity discrimination as a function of frequency and sensation level. *J Acoust Soc Am* 1977;61:169–77.
- Makela JP, Hari R, Linnankivi A. Different analysis of frequency and amplitude modulations of a continuous tone in the human auditory cortex: a neuromagnetic study. *Hear Res* 1987;27:257–64.
- Martin BA, Boothroyd A. Cortical, auditory, evoked potentials in response to changes of spectrum and amplitude. *J Acoust Soc Am* 2000;107:2155–61.
- McCandless GA, Rose DE. Evoked cortical responses to stimulus change. *J Speech Hear Res* 1970;13:624–34.
- Moore BC, Peters RW, Kohlrausch A, van de Par S. Detection of increments and decrements in sinusoids as a function of frequency, increment, and decrement duration and pedestal duration. *J Acoust Soc Am* 1997;102:2954–65.
- Naatanen R, Picton T. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. *Psychophysiology* 1987;24:375–425.

- Neuhoff JG. Perceptual bias for rising tones. *Nature* 1998;395:123–4.
- Nuwer MR, Comi G, Emerson R, Fuglsang-Frederiksen A, Guerit JM, Hinrichs H, et al. IFCN standards for digital recording of clinical EEG. International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol* 1998;106:259–61.
- Pantev C, Hoke M, Lehnertz K, Lutkenhoner B. Neuromagnetic evidence of an amplitopic organization of the human auditory cortex. *Electroencephalogr Clin Neurophysiol* 1989;72:225–31.
- Pantev C, Bertrand O, Eulitz C, Verkindt C, Hampson S, Schuierer G, et al. Specific tonotopic organizations of different areas of the human auditory cortex revealed by simultaneous magnetic and electric recordings. *Electroencephalogr Clin Neurophysiol* 1995;94:26–40.
- Phillips DP, Semple MN, Calford MB, Kitzes LM. Level-dependent representation of stimulus frequency in cat primary auditory cortex. *Exp Brain Res* 1994;102:210–26.
- Rose JE, Brugge JF, Anderson DJ, Hind JE. Phase-locked response to low-frequency tones in single auditory nerve fibers of the squirrel monkey. *J Neurophysiol* 1967;30:769–93.
- Rose JE, Hind JE, Anderson DJ, Brugge JF. Some effects of stimulus intensity on response of auditory nerve fibers in the squirrel monkey. *J Neurophysiol* 1971;34:685–99.
- Spoor A, Timmer F, Odenthal DW. The evoked auditory response (EAR) to intensity modulated and frequency modulated tones and tone bursts. *Int Audiol* 1971;33:367–77.
- Stufflebeam SM, Poeppel D, Rowley HA, Roberts TP. Peri-threshold encoding of stimulus frequency and intensity in the M100 latency. *Neuroreport* 1998;9:91–4.
- Turner CW, Zwislocki JJ, Filion PR. Intensity discrimination determined with two paradigms in normal and hearing-impaired subjects. *J Acoust Soc Am* 1989;86:109–15.
- von Békésy G. Experiments in hearing. New York: McGraw-Hill; 1960.
- Winter IM, Palmer AR. Intensity coding in low-frequency auditory-nerve fibers of the guinea pig. *J Acoust Soc Am* 1991;90:1958–67.
- Woods DL, Alain C, Covarrubias D, Zaidel O. Frequency-related differences in the speed of human auditory processing. *Hear Res* 1993;66:46–52.
- Zar JH. Biostatistical analysis. 4th ed. Upper Saddle River: Prentice Hall; 1999.