

Lateral inhibition in the auditory cortex: An EEG index of tinnitus?

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Auditory ERPs were recorded from eight tinnitus patients and 12 controls. Tone pips of 1000 and 2000 Hz, as well as the patient's tinnitus pitch (around 4000 Hz) were used. Controls received tone pips at 1000, 2000, and 4000 Hz. Tones were presented at 30, 36, 42, 48 and 54 dB/SL. The intensity dependence of the auditory N100 was calculated for each frequency in each group. Patients showed a steeper response to the tinnitus frequency than responses to the

4000 Hz tone in controls. In contrast, intensity-dependence to the 2000 Hz tones was significantly decreased in patients (two-tailed Wilcoxon-Mann-Whitney U-test, $p < 0.05$). Responses to the 1000 Hz tones were similar for both groups. This reduced intensity dependence is hypothesized to result from lateral inhibition arising from tinnitus related activity in the 4000 Hz isofrequency region. *NeuroReport* 13:443–446 © 2002 Lippincott Williams & Wilkins.

Key words: Intensity dependence; Lateral inhibition; Low threshold spikes; N100; Thalamocortical dysrhythmias

INTRODUCTION

Tinnitus is a common disorder of the auditory system affecting about 17% of the general population in the USA and up to 33% of the elderly. About a quarter of these are sufficiently bothered by their tinnitus to seek professional help [1]. Tinnitus is a phantom perception and hence not associated with any external auditory event. In the past, tinnitus was viewed as originating in the auditory periphery [2–4]. More recently, neural correlates of the disorder have been found in central auditory structures [5–8]. Such findings do not preclude the causal origin for the development of tinnitus from occurring in the periphery.

The fact that tinnitus is consciously perceived as a sound suggests that neural activity must occur in CNS auditory structures and pathways. Furthermore, the persistent activation of cortical tissue by tinnitus is assumed to compete for neural substrate with normal stimulus-induced activity in the primary auditory cortex. In order to compensate, the processing of auditory stimuli in the presence of tinnitus-related activity may require an increase in firing rate of neurons, the use of more neural substrate, or a combination of both. We have hypothesized that these compensatory mechanisms lead to an increased intensity dependence in responses to external auditory events. Since the magnitude of the largest possible response is limited, the presence of tinnitus may lead to a steeper gain function in the responsiveness of the primary auditory cortex and a decrease in the dynamic range of hearing sensitivity.

A correlate of this steeper gain function has been reported by Norena and colleagues [5], who observed an increased intensity dependence of the N100 auditory evoked potential in tinnitus subjects. The N100 is known to increase in amplitude and decrease in latency with increasing stimulus intensity [9–11]. This intensity dependence of the N100 response is associated with the tangentially oriented dipole of the N100 component that is recorded primarily along midline sites. According to studies of dipole source analysis [12,13], this tangentially oriented dipole reflects mainly activity of the primary auditory cortex. In contrast, the radially oriented dipole reflects activity of the secondary auditory cortex in the more lateral parts of the temporal lobe [14].

Since it is assumed that tinnitus related activity involves the primary auditory cortex, the dependent measure for this study was the midline N100 component. This component appears to be a good index for tinnitus because it reflects stimulus properties as well as attention and the psychological state of the subjects, both of which are presumed to contribute to tinnitus [1].

Since tinnitus perception is subjective by its very nature, there have been no objective measurements that could be related to it until very recently [15]. A diagnosis of tinnitus has had to rely on a variety of questionnaires [16,17]. On the other hand, changes in the dynamic response characteristics of the auditory cortex by tinnitus could be used as a basis for an objective diagnostic tool.

MATERIALS AND METHODS

Subjects: Eight subjects suffering from tinnitus (mean (\pm s.d.) age 46.8 ± 11.7 years) and twelve control subjects (mean age 39.1 ± 10.7 years) were studied. The hearing thresholds of all subjects were determined using routine pure tone audiometry. Patients suffering from tinnitus were referred from the Head and Neck Surgery Clinic at the UCSD Medical Center, while control subjects were recruited from the population of the UCSD campus. An effort was made to match the age of the control subjects to the age of the tinnitus subjects. Informed consent was obtained from all subjects. The Institutional Review Board of the University of California, San Diego approved the experimental procedures.

Tinnitus matching procedure: A subject's tinnitus perception was characterized prior to every recording session by matching the pitch of their tinnitus to the frequency of a sine tone. In our experience, this matching procedure has proven vulnerable to octave confusions, i.e. some subjects matched their tinnitus pitch consistently at two different frequencies, depending on whether the matching procedure was begun at a frequency higher or lower than their tinnitus pitch. These frequencies generally were one or two octaves apart. If this was the case, we presented both frequencies to the subject alternately and asked which one was a better match.

EEG experiments: EEG was collected using standard methods. Data were recorded from 15 electrode sites mounted on an elastic cap and located over the following scalp sites: F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, T3, T4, T5, T6, O1, and O2 (according to the modified International 10–20 System). Eye movement artifact, particularly blinks, was recorded from vertical and/or horizontal EOG electrodes. In order to maintain compatibility with previous studies [5], all electrode sites were referred to linked mastoids. Within each series, 80 stimuli of different intensities, for a total of 400 stimuli, were presented in random order and at intervals varying randomly between 1 and 3 s. The EEG was amplified by a factor of 10000 and bandpass filtered between 0.01 and 100 Hz using 3 dB down-filter skirts. Analog signals were recorded and digitized at a sampling rate of 250 Hz.

The auditory stimuli were pure tones generated by a function generator. A specially designed programmable logarithmic amplifier that was controlled in real time by a stimulus presentation and data collection program set the intensity of each stimulus. Tone pips of 200 ms duration were presented at five different intensities (30, 36, 42, 48 and 54 dB SL) through insert earphones (Eartone 3A transducers with Earlink foam eartips). We recorded auditory event related potentials (ERP) in response to tones at three frequencies. For the tinnitus subjects these frequencies were 1000 Hz, 2000 Hz and their tinnitus-match frequency. In non-tinnitus subjects 4000 Hz substituted for the tinnitus frequency.

Data analysis: The EEG data were analyzed using a two-stage approach. In the first stage, traditional artifact rejection was employed to remove trials with amplifier blocking and those that contained eye movement artifacts.

The artifact-free EEG epochs for each intensity and condition were then averaged and the amplitudes of the N100 components measured. Based on these data, intensity-amplitude functions were computed for all 15 electrode sites. These were used to characterize an individual's responsiveness to specific tonal frequencies.

The peak amplitudes of the N100 component were measured and plotted against the stimulus intensity. A linear regression was calculated, and its slope was used to characterize the intensity dependence of the N100 component recorded from the midline electrode sites Fz, Cz and Pz. For each stimulus frequency, these intensity-amplitude functions were compared between the tinnitus and control groups using a two-tailed Wilcoxon-Mann Whitney U-test ($p < 0.05$). Since three tests were performed for each stimulus condition, a correction for multiple comparisons based on the binomial distribution [18] was performed by calculating α' :

$$\alpha' = \sum_{i=n}^k (k/i)\alpha^i \times (1 - \alpha)^{k-i}$$

where k is the number of tests performed, n the number of tests that showed a significant result and α the significance level of the individual tests. Differences in the intensity-amplitude functions were considered significant when α' was less than the desired significance level, i.e. $\alpha' < 0.05$.

RESULTS

The results of the audiometric testing are shown in Table 1. An example of the N100 waveforms and its intensity-amplitude function is shown in Fig. 1. Comparison of the slopes of the intensity-amplitude functions between the tinnitus and control groups showed that the N100 responses from tinnitus patients to tones at their tinnitus frequency were slightly more intensity dependent (i.e. steeper slopes) than those of non-tinnitus controls to 4000 Hz tones (Fig. 2c). In contrast, responses from the tinnitus group were significantly ($p < 0.05$) less intensity dependent to 2000 Hz tones than responses from the non-tinnitus control subjects (Fig. 2b). The intensity dependence of responses to 1000 Hz tones is nearly identical in tinnitus and control subjects (Fig. 2a). Taken together these findings strongly suggest that tinnitus induces specific changes to N100 intensity dependence.

DISCUSSION

The present results support the hypothesis that the presence of tinnitus related activity changes the intensity dependence of the N100 in a frequency specific manner. The experimental data show statistically significant reductions in the intensity dependence of the N100 in response to 2000 Hz tones and a non-significant increase in the intensity dependence of responses to the tinnitus frequency tones (4000 Hz tones). It is our contention that tinnitus related activity produces an increase in firing rate of neurons or activation of more neural substrate. This, we believe, is reflected in the enhanced intensity dependence to tones at that frequency. Furthermore, enhanced activation of this isofrequency region causes inhibition of neighboring re-

Table I. Results of subject audiometric testing.

	Hearing loss					
	Right			Left		
	1 kHz	2 kHz	4 kHz	1 kHz	2 kHz	4 kHz
Tinnitus						
Within normal limits	7	6	4	8	7	3
Mild	1	1	1	0	1	5
Moderate	0	1	3	0	0	0
Controls						
Within normal limits	12	12	10	12	12	11
Mild	0	0	1	0	0	1
Moderate	0	0	1	0	0	0

gions via lateral inhibitory mechanisms. This is reflected in the reduced intensity dependence to neighboring tones.

Our working model of tinnitus is drawn from a recently proposed neurophysiological model of the disorder [19] in which tinnitus arises as a consequence of thalamocortical dysrhythmias. More precisely, auditory nuclei in the thalamus interact to establish a reverberating loop in which neuronal activity originating from this reverberating loop gets transmitted to the auditory cortex, where it gives rise to the perception of tinnitus. Such reverberating loops are established through disinhibition of cells in the thalamus, which occurs when thalamic relay cells are hyperpolarized by a lack of normal depolarizing sensory input. The action

potentials generated by this hyperpolarizing mechanism, or low threshold spikes (LTS), usually occur in rhythmic bursts.

A computational model of tinnitus recently proposed by Langner *et al.* [20] accounts for how a decreased auditory input resulting from a peripheral hearing deficit can give rise to a specific tinnitus pitch. According to this model, the detection of tinnitus-related activity will be facilitated by mechanisms of lateral inhibition in the central auditory system. These will act to confine the neural activity causing the phantom perception to regions representing distinct frequencies and increase the contrast between the tinnitus-related activity and the spontaneous activity in adjacent regions.

Another indication that tinnitus related activity is confined to certain isofrequency regions of the auditory cortex comes from the fact that most tinnitus perceptions have distinct pitch. Furthermore, this pitch is often related to the underlying pathology. For example, noise induced tinnitus tends to have a pitch near 4000 Hz [21]. In cases where the tinnitus is perceived as tonal, tinnitus-related activity in the auditory cortex can be assumed to be limited to isofrequency regions that correspond to the tinnitus pitch. Consequently, the changes in the intensity dependence of the midline auditory N100 response can be expected to be frequency specific.

Based on these models, a likely explanation for our findings is that tinnitus-related activity in the 4000 Hz isofrequency region gives rise to lateral inhibition and thereby inhibits responses from the adjoining 2000 Hz isofrequency region of the primary auditory cortex. This produces decreased intensity dependence of the auditory evoked potential in response to 2000 Hz tones. This lateral inhibition effect must be limited in range such that responses to tones that are sufficiently different from the tinnitus frequency are not affected. Indeed, the intensity dependence of responses to 1000 Hz tones is nearly the same in tinnitus and control subjects. This last finding contrasts with the increased intensity dependence of the N1/P2 component reported by Norena *et al.* [5]. However, since the N1/P2 complex is thought to be generated by equivalent dipoles representing the primary and secondary auditory cortices, whereas the N100 observed in this study is thought to be generated by equivalent dipoles representing only the primary auditory cortex, the contribution of the secondary

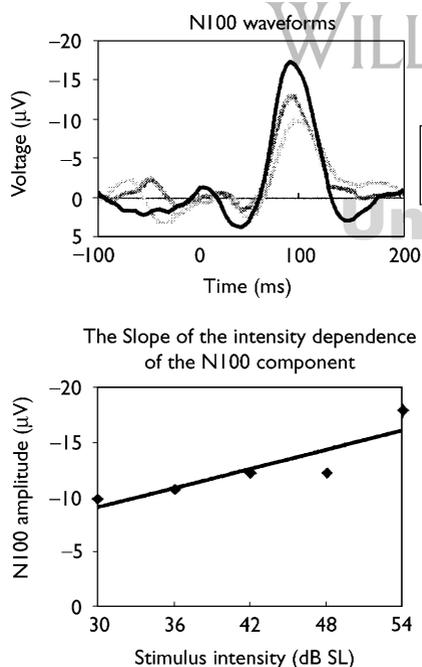


Fig. 1. Top: Waveforms of N100 responses to 1 kHz tones presented at 30 dB/SL, 42 dB/SL and 54 dB/SL. Bottom: N100 Amplitudes plotted against stimulus intensity to show the intensity dependence function. The slope of the linear regression was used as a measure of cortical responsiveness.

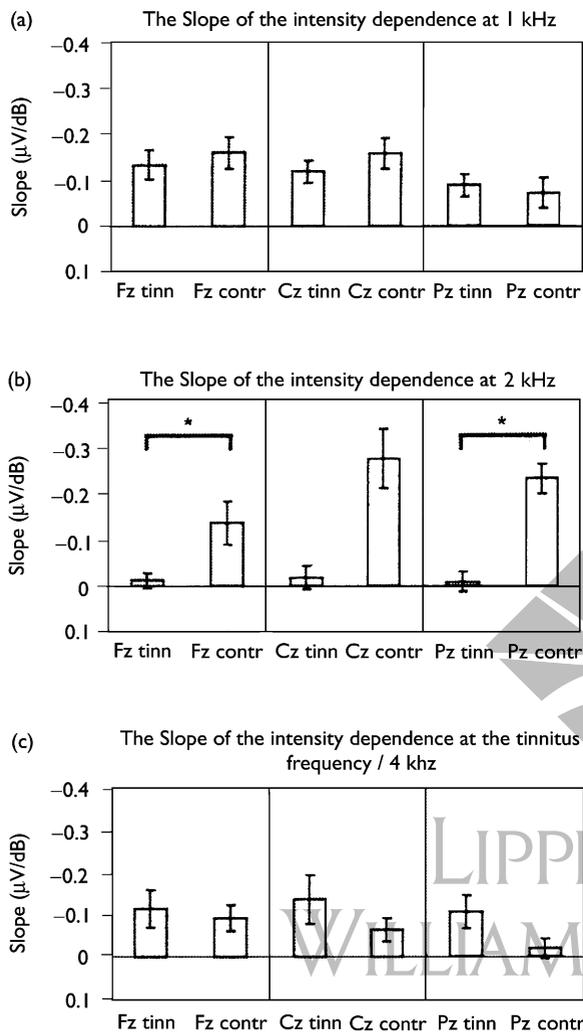


Fig. 2. Comparison of the slopes of the intensity dependence between the tinnitus and control groups. (a) Responses to 1 kHz tones. (b) Responses to 2 kHz tones. (c) Responses to tinnitus frequency/4 kHz tones.

auditory cortex may contribute to the higher intensity dependence observed by Norena *et al.* Another factor that can be expected to influence the intensity dependence of the N100 is hearing loss. As shown in Table 1, about half of the tinnitus subjects had some hearing loss at their tinnitus frequency. This hearing loss could lead to recruitment, i.e. increased loudness growth in response to higher intensity stimuli. Recruitment may be an alternative explanation for the increased intensity dependence of the N100 response at the tinnitus frequency. However, hearing for the tinnitus subjects was less impaired at 2000 Hz, i.e. an octave lower

than the tinnitus, so that hearing loss cannot account for the changed dynamics in N100 responses to these tones. Furthermore, the effect of hearing loss as described above would be to cause an increase of the N100 intensity dependence rather than the observed decrease.

CONCLUSIONS

The present results suggest that tinnitus related activity in the primary auditory cortex changes the characteristics of the N100 component of the auditory evoked potential in a frequency specific manner. In tinnitus subjects responses to tinnitus frequency tones are slightly more dependent on stimulus intensity than in controls, while responses to 2000 Hz tones, i.e. approximately one octave below the tinnitus frequency are significantly less dependent on stimulus intensity. The lack of intensity dependence in responses to 2000 Hz tones is most likely caused by lateral inhibition in the auditory cortex arising from the tinnitus related activity. The observed changes in the dynamic properties of the N100 response is a way of demonstrating tinnitus related activity in the central neural system and may provide the basis for an objective tinnitus diagnostic tool in the future.

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