International Tinnitus Journal, Vol. 12, No. 1, 9–16 (2006)

Arousal and Attention Deficits in Patients with Tinnitus

John Dornhoffer,[1] Christopher Danner,[1] Mark Mennemeier,[2] Donna Blake,[1] and Edgar Garcia-Rill[2]

[1]*Department of Otolaryngology–Head and Neck Surgery and* [2]*Department of Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, Little Rock, Arkansas*

Abstract: We investigated the effects of tinnitus on measures of arousal and attention at various levels of the neuraxis to derive a profile of the pathophysiology of tinnitus. Individuals with tinnitus of at least 6 months' duration (14 male, 15 female) and healthy controls (14 male, 21 female) were tested for arousal and habituation to repetitive stimulation at the brainstem-thalamus level by measuring the P50 potential, a scalp-recorded, auditory-evoked response, using pairs of click stimuli. We used the psychomotor vigilance task, a reaction-time test, to assess attentional processes mediated by thalamocortical functions. We then correlated deficits in arousal and attention, as measured by these tests, with perceived tinnitus severity. Results showed no difference between tinnitus patients and controls in level of arousal or habituation to repetitive sensory stimulation, as measured by the amplitude of the P50 potential and the ability to suppress a second, closely paired stimulus, respectively. However, reaction-time assessments showed that patients with tinnitus have attentional deficits relative to controls ($p = .02$). We found no significant correlation between sleep disturbance or tinnitus severity and reaction-time testing.

Key Words: arousal; attention; psychomotor vigilance task; P50 potential; reaction-time testing; tinnitus

Subjective tinnitus, the perception of sound in the absence of acoustic stimulation, is a common phenomenon affecting approximately 17% of the general population in the United States [1–3]. Approximately one-fourth of these individuals seek professional help owing to associated mood, sleep, and concentration disturbances [1–3]. The exact mechanisms of tinnitus generation and the related central nervous system dysfunction are unknown, rendering diagnosis and treatment difficult and often empirical. Most believe that the inciting event for tinnitus generation lies in cochlear or auditory nerve dysfunction, but the perception of tinnitus is traced back to central mechanisms in most cases [2,4–7].

Although many tinnitus sufferers complain of poor concentration, neuropsychological testing has revealed that the cognitive inefficiency appears to be associated with the control of attention, especially the inhibition of attention task–irrelevant activity [8–10]. This is believed to be related to difficulties in habituation to the perceived tinnitus sound, with a resulting sensory gating deficit. *Habituation* can be defined as the reduction of perception after repeated exposure to a repetitive stimulus, but whether the mechanism of auditory habituation resides in the primary auditory pathway, in subcortical areas, or at higher cognitive levels is not known [11]. Positron emission tomography (PET) has revealed that habituation to auditory stimuli probably occurs in subcortical structures, perhaps at the level of the thalamus, suggesting the importance of the lower levels of the neuraxis (brainstem and thalamus) in this process [11].

In this study, the pathophysiology of tinnitus was investigated by assessing various levels of the neuraxis

Reprint requests: John Dornhoffer, MD, Department of Otolaryngology–Head and Neck Surgery, University of Arkansas for Medical Sciences, 4301 West Markham, MS 543, Little Rock, AR 72205. Phone: (501) 686-5016; Fax: (501) 686-8029; E-mail: DornhofferJohnL@uams.edu

Presented at the Combined Otolaryngological Spring Meeting, Chicago, IL, May 19–22, 2006.

for arousal and attention. The P50 potential, a scalp-recorded, auditory-evoked response that occurs at a latency of 40–70 milliseconds in humans, was used to assess arousal and habituation at the brainstem-thalamus level of the neuraxis. The P50 potential is sleep state–dependent, habituates at low frequencies of stimulation, and is blocked by the muscarinic antagonist scopolamine [12–14] (and thus is thought to be generated, at least in part, by the reticular activating system). Though the amplitude of the P50 potential is a measure of the level of arousal, a paired-stimulus paradigm can be used to measure habituation, which is part of the process of sensory gating [15,16].

The psychomotor vigilance task (PVT) was used as a measure of attention. Assessment of simple reaction time (RT) is the most commonly used measure of thalamocortically mediated attentional systems related to vigilance or sustained attention [17–19]: Arousal falls as vigilance continues, and attention is required to boost arousal and support performance [20]. The PVT is a test of behavioral alertness and involves a simple (not choice) reaction-time test designed to evaluate the ability to sustain attention and to respond in a timely manner to salient signals [21]. The PVT was designed to be simple to perform, free of a learning curve or influence from acquired skills (aptitude, education), and highly sensitive to an attentional process that is fundamental to normal behavioral awareness.

In an attempt to determine any association between deficits in arousal and attention and the magnitude of the tinnitus complaint, we correlated the findings of these tests with the perceived severity of tinnitus based on tinnitus severity and sleep disturbance questionnaires.

MATERIALS AND METHOD

Study Subjects

We identified and recruited patients with tinnitus (n = 29) and controls without a history of tinnitus (n = 35) from the Otolaryngology Clinic at the University of Arkansas for Medical Sciences. All tinnitus patients reported experiencing the presence of their phantom auditory perception for at least 6 months. Patients or controls with significant neurological disease, acoustic neuromas or glomus tumors, active Ménière's disease, or profound hearing loss (> 90 dB at 4,000 Hz) were excluded from the study. Individuals on psychotropic medicines, including antidepressants, anticonvulsants, or sleep aids, also were excluded. This study was approved by the Institutional Review Board at the University of Arkansas for Medical Sciences.

Tinnitus Severity Assessments

All subjects completed a tinnitus severity index [22], which was a modification of the Colorado Otolaryngology Associates Severity Index (Fig. 1). The measures included a numerical scoring system for questions related to the perceived evaluation of tinnitus discomfort, which could then be used in the statistical evaluation of this parameter. We also administered the insomnia portion of the sleep disorders questionnaire to both tinnitus and control groups to assess functional impairment in sleep function [23].

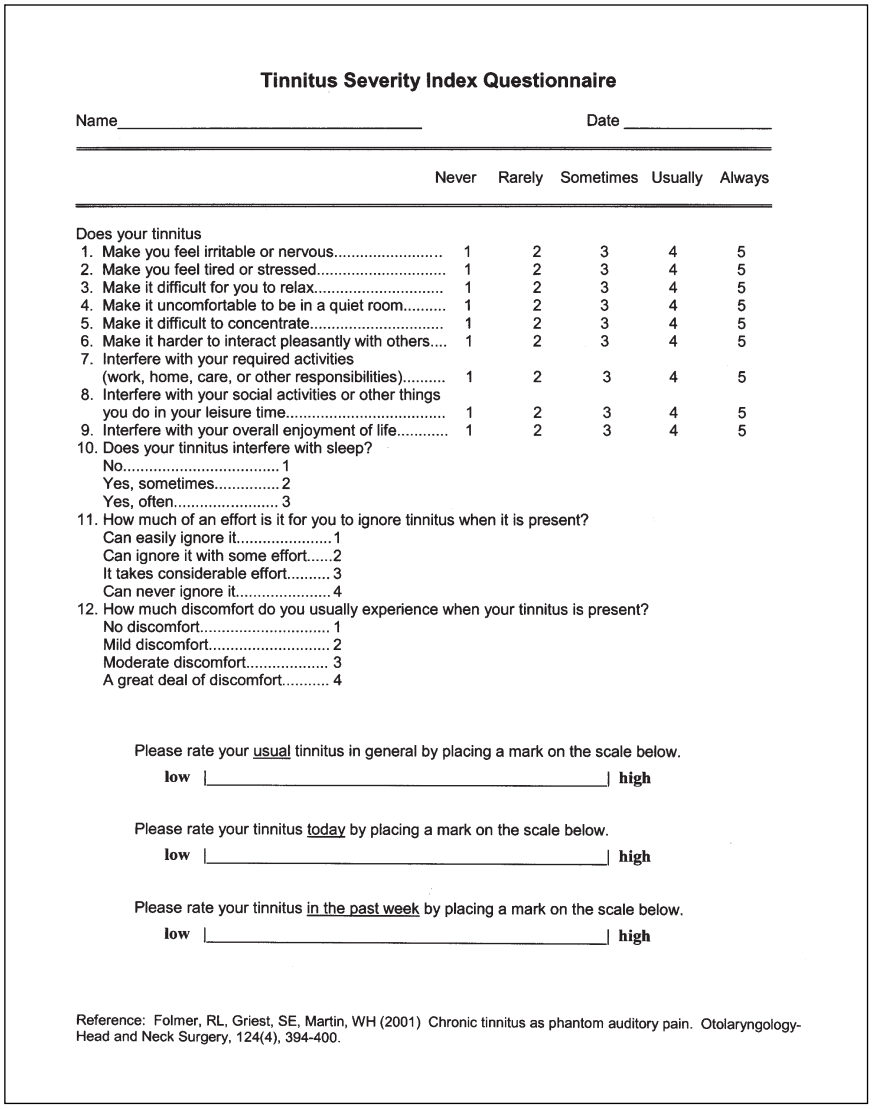
Recordings of the P50 Potential

We carried out recordings of the P50 potential using a paired-stimulus paradigm as previously described [12–16,24,25]. Briefly, we recorded the P50 potential at the vertex referenced to a frontal electrode using gold-plated surface electrodes. We monitored eye movements (electrodes placed diagonally across one eye) and jaw movements (electrodes placed on the masseter muscle and chin) for interference with the P50 potential waveform. Trials with significant eye or jaw movement artifacts were eliminated from the average. We used a subclavicular ground. Each channel was led to a Grass Instruments P511 amplifier (Quincy, MA) with a high-resistance input stage.

We placed headphones on each study subject, and the test stimulus was a rarefaction click of 0.1-millisecond duration, set at 50 dB above hearing threshold. (We performed a hearing test just prior to the P50 recording sessions.) Three testing sessions consisted of paired click stimuli at 250-, 500-, and 1,000-millisecond interstimulus intervals (ISI), respectively. We delivered pairs of clicks once every 5 seconds until 64 pairs of evoked potentials were acquired, averaged, and stored by the computer. The P50 potential was identified as the largest-amplitude positive wave occurring between 40 and 70 milliseconds. We measured the amplitude of the P50 potential as previously described [12–14,24–31], and we determined habituation by calculating the ratio of the P50 potential induced by the second stimulus of a pair to the P50 potential induced by the first stimulus of a pair, expressed as a percentage.

The Psychomotor Vigilance Task

The PVT assesses simple RT by measuring the amount of time taken by a subject to respond to a visual or auditory stimulus. The auditory stimulus was a >90-dB sound pressure level tone of 1,000 Hz; no patient complained of discomfort at this level. The visual cue comprised blinking numbers, and subjects were asked to



Tinnitus Severity Index Questionnaire

Name_____ Date _____

	Never	Rarely	Sometimes	Usually	Always
Does your tinnitus					
1. Make you feel irritable or nervous	1	2	3	4	5
2. Make you feel tired or stressed	1	2	3	4	5
3. Make it difficult for you to relax	1	2	3	4	5
4. Make it uncomfortable to be in a quiet room	1	2	3	4	5
5. Make it difficult to concentrate	1	2	3	4	5
6. Make it harder to interact pleasantly with others	1	2	3	4	5
7. Interfere with your required activities (work, home, care, or other responsibilities)	1	2	3	4	5
8. Interfere with your social activities or other things you do in your leisure time	1	2	3	4	5
9. Interfere with your overall enjoyment of life	1	2	3	4	5

10. Does your tinnitus interfere with sleep?
    No 1
    Yes, sometimes 2
    Yes, often 3
11. How much of an effort is it for you to ignore tinnitus when it is present?
    Can easily ignore it 1
    Can ignore it with some effort 2
    It takes considerable effort 3
    Can never ignore it 4
12. How much discomfort do you usually experience when your tinnitus is present?
    No discomfort 1
    Mild discomfort 2
    Moderate discomfort 3
    A great deal of discomfort 4

Please rate your usual tinnitus in general by placing a mark on the scale below.

low |_____| high

Please rate your tinnitus today by placing a mark on the scale below.

low |_____| high

Please rate your tinnitus in the past week by placing a mark on the scale below.

low |_____| high

Reference: Folmer, RL, Griest, SE, Martin, WH (2001) Chronic tinnitus as phantom auditory pain. Otolaryngology-Head and Neck Surgery, 124(4), 394-400.

Figure 1. Tinnitus severity index questionnaire used in study.

press with the thumb or forefinger of the dominant hand a response button on a remote control as soon as the stimulus was perceived, hence stopping the counter and displaying the RT in milliseconds. The ISI on the task varied from 2 to 10 seconds. The entire PVT test time lasted 10 minutes, with approximately 80 RTs recorded per trial. Software then was used to analyze the following parameters: (1) *frequency of lapses*, which refers to the number of times that a subject failed to respond to the signal or failed to respond in a timely manner (>400 msec); (2) *duration of lapse domain*, which refers to shifts in lapse duration calculated from the slowest 10% RTs, a measure that reflects vigilance-response slowing; (3) *optimum response times*, which are the average of the fastest 10% RTs per trial and reflect the very best performance an operator is capable of producing; (4) *fatigability function*, which refers to the vigilance decrement function or the extent to which subjects maintained performance across time on task; and (5) *false response frequency*, which refers to the number of responses that were initiated when no stimulus was present. Circadian effects were controlled by performing the test at the same time of day (late morning) for all subjects.

RESULTS

Study Population

A total of 64 subjects were enrolled in the study: 29 individuals with chronic tinnitus (14 male, 15 female) and 35 control subjects (14 male, 21 female). The age of the tinnitus patients ranged from 34 to 78 years (mean, 54.8 years), and the age of the control subjects ranged from 30 to 80 years (mean, 49.5 years). No significant difference in age was observed between the control group and the tinnitus group: $t(62) = 1.68$; $p = .10$.

Table 1. P50 Amplitude and Percent Habituation in Tinnitus Patients and Controls

	P50 Amplitude[a] ± SD			Percent Habituation ± SD[b]		
ISI (msec)	Controls (n = 35)	Tinnitus Patients (n = 28)	*p* Value	Controls (n = 35)	Tinnitus Patients (n = 28)	*p* Value
250	2.2 ± 1.4	2.1 ± 0.9	0.8	23.0 ± 32.1	21.4 ± 29.1	0.8
500	1.9 ± 1.2	2.1 ± 0.9	0.6	34.8 ± 33.6	34.3 ± 29.7	1.0
1,000	1.9 ± 1.3	1.8 ± 0.9	0.8	49.9 ± 34.3	65.5 ± 39.8	0.1
Average P50	1.9 ± 1.2	2.0 ± 0.8	0.9			

ISI = interstimulus interval; SD = standard deviation.
[a] Defined as the largest-amplitude positive wave occurring between 40 and 70 milliseconds.
[b] Defined as the ratio of the P50 potential induced by the second stimulus of a pair to the P50 potential induced by the first stimulus of a pair, expressed as a percentage.

Differences in Arousal and Habituation (P50 Potential)

The results for the P50 potential recordings are shown in Table 1. One tinnitus subject was excluded owing to an inability to obtain replicable waveforms, leaving 28 tinnitus patients for assessment. Control subjects and tinnitus patients showed no difference in level of arousal, as measured by the amplitude of the P50. Control subjects and tinnitus patients likewise did not show significant differences in habituation as measured by the ability to suppress a second, closely paired stimulus, regardless of ISI.

Differences in Sustained Attention

The results for the PVT are shown in Table 2. Controls and tinnitus patients did not show a significant difference in frequency of lapses (RTs >400 msec); optimum response times (fastest 10% RTs); fatigability; or false response frequency (responding without stimulus). However, we found significant differences in the duration of lapse domain (slowest 10% of RTs) between the tinnitus group and controls [$t(64) = 2.31$; $p = .02$], with tinnitus patients having RTs longer than those of controls.

Table 2. Results of Reaction-Time Testing in Tinnitus Patients and Controls

Reaction Times (msec)	Controls (n = 35)	Tinnitus Patients (n = 29)	*p* Value
Mean	205.2 ± 33.5	217.4 ± 49.0	.2
Fastest 10%	155.2 ± 25.8	154.9 ± 28.6	1.0
Slowest 10%	318.8 ± 70.5	380.3 ± 136.8	.02*
Fatigability	–0.013 ± 0.1	–0.005 ± 0.1	.7
False starts	0.5 ± 1.8	0.8 ± 1.4	.6

* Statistically significant.

Tinnitus Severity

We found no significant difference between controls and tinnitus patients with regard to the insomnia portion of the sleep disorders questionnaire ($p = .5$). Table 3 shows the correlations between the total score on the tinnitus questionnaire, the score on the sleep disorders questionnaire, and the results for the PVT. For the purposes of this analysis, we used data only from tinnitus patients. As shown, we found no significant correlation between sleep disturbance and the PVT but did note a significant association with irritability and discomfort with tinnitus and the number of false starts.

Table 3. Pearson Correlations Between Psychomotor Vigilance Task Variables and Tinnitus Severity Self-Assessment and Insomnia Scores

Complaint	Mean RT	Fastest 10% RT	Slowest 10% RT	Fatigability	False Starts
Loudness[a]					
r	0.119	0.102	0.191	0.042	0.148
p	.538	.600	.322	.830	.442
Discomfort[a]					
r	0.094	0.016	–0.021	0.123	0.410
p	.627	.933	.914	.525	.027
Irritability[a]					
r	–0.012	–0.054	–0.104	0.173	0.367
p	.951	.781	.591	.370	.050
Sleep problems[a]					
r	–0.162	–0.247	–0.160	0.128	0.358
p	.401	.197	.406	.510	.057
Life interference[a]					
r	–0.046	–0.062	–0.156	0.283	0.248
p	.813	.750	.420	.136	.195
Insomnia[b]					
r	–0.203	–0.200	–0.233	0.021	0.264
p	.376	.385	.310	.928	.248

RT = reaction time.
[a] Taken from tinnitus severity index questionnaire [22], modified from Colorado Otolaryngology Associates PC Tinnitus Questionnaire, 5/1/03.
[b] Taken from sleep disorders questionnaire [23].

DISCUSSION

Several theories concerning tinnitus generation have been proposed, such as the discordant damage theory [32], spontaneous otoacoustic emissions [11], thalamocortical dysrhythmia [33,34], and maladaptive cortical reorganization after peripheral injury, analogous to the model of chronic pain [5,7,35,36]. Though none of these theories is universally accepted, most propose that the development of chronic tinnitus is related to central nervous system dysfunction, even though peripheral injury in the cochlea is the inciting event. A working model that appears to explain many of the findings in tinnitus suggests that tinnitus is generated by lack of inhibition of auditory nuclei 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 usually occur in rhythmic bursts, which can lead to the establishment of a reverberating loop between the thalamus and the auditory cortex, where tinnitus is perceived. These thalamocortical dysrhythmias then lead to or facilitate maladaptive cortical reorganization and the phantom perception of sound in a chronic fashion [4,5,33–36]. That is, some of these theories posit that tinnitus is neurogenic, or centrally generated.

Individuals with tinnitus frequently report poor mental concentration, but neuropsychological testing reveals that the effect of tinnitus on cognitive processing is likely to manifest selectively in tasks involving the control of attention [8–10]. External noise has been demonstrated to have a negative impact on performance during dual tasks involving sustained attention, especially when the stimulus is varied. In the case of tinnitus, noise may be generated internally rather than externally. In fact, incessant perception of sound is an agonizing feature of tinnitus. Habituation to repeated sensory stimuli occurs after an initial orienting. Hallam et al. [37] proposed that tinnitus represents a fundamental deficit in habituation, wherein the internally generated stimulus continues to elicit unattenuated orienting responses, thus claiming constant attention. The failure to habituate may derive from internal factors, such as readiness to attend or tonic arousal, or may be related to the perceived novelty of the internally generated noise. Tinnitus may also be considered to be a varying stimulus due to environmental masking, with some tinnitus representing a complex mix of several sounds.

In this study, the P50 potential was used as a measure of arousal and habituation at the brainstem-thalamus level. Orienting involves arousal systems the function of which was reflected by the initial P50 potential amplitude; habituation was reflected by a reduction of the P50 amplitude to the second stimulus. A consequence of habituation is the process of sensory gating, which represents a critical function to focus attention and filter out extraneous information, and can be derived from the use of paired stimuli to test the level of habituation in the system being studied. The P50 potential has three main characteristics: First, it is present during waking and rapid eye movement sleep but not during deep slow-wave sleep [14]; therefore, it is sleep state–dependent, occurring during cortical electroencephalographic synchronization of fast oscillations but not during cortical synchronization of slow oscillations. Second, it is blocked by the muscarinic cholinergic antagonist scopolamine and, therefore, may be mediated, at least in part, by cholinergic neurons [14]. Third, it undergoes rapid habituation at stimulation rates greater than 2 Hz; therefore, it is not manifested by a primary afferent pathway but perhaps by multisynaptic, low-security synaptic elements of the reticular activating system relayed to the cortex through the intralaminar thalamus [14]. That is, the brainstem-thalamus is the main relay responsible for the P50 potential so that disorders that involve thalamic structures may exhibit dysregulation of the P50 potential.

In our study, we saw no significant difference in the overall amplitude of the P50 potential or habituation between individuals with tinnitus and age-matched controls. This suggests that tinnitus patients have no impairment in their level of tonic arousal and that, though tinnitus represents a fundamental deficit in habituation, the deficit appears not to be at the brainstem-thalamus level. Our findings also indicate that patients with tinnitus have a normal ability to habituate to externally generated repetitive stimuli.

The main deficit that distinguished tinnitus patients from control subjects in our study was a failure to sustain optimal performance (vigilance) over time, as reflected by the duration of their slowest RTs during PVT testing. Attentional vigilance involves the modulation of thalamic processes related to arousal (i.e., nonspecific projections from the intralaminar thalamus) by a fronto-cingulo-temporo-parietal network [17,38–40]. RT during a vigilance task is a classic measure of attentional influences on intrinsic alertness [17–19]: Arousal falls as vigilance continues, and attention is required to boost arousal and support performance [20]. Sustained attention, or vigilance, as measured by the PVT, is an extremely useful measure of the thalamocortically mediated attentional system. Although significant sleep deprivation leads to a global reduction in the reaction-time parameters of the PVT, the lapses (RTs $>$500 msec) and the 10% slowest RTs are the most sensitive measures of vigilance.

In this study, we noted no significant difference between controls and individuals with tinnitus in the 10% fastest RTs, lapses, fatigability, or false starts, but we

did detect a significant difference in the 10% slowest RTs ($p = .02$). This pattern of results is similar to one observed by Hallam et al. [8] in tinnitus patients during reaction-time testing using dual-task conditions. Although sleep pressure is known to reduce performance, no difference was seen in sleep disturbance in the tinnitus patients versus controls, and no correlation was seen with tinnitus severity or sleep disturbance and the PVT results, with the exception of the number of false starts seen in individuals reporting increased irritability. These findings suggest that the vigilance deficit observed in patients with tinnitus may be linked to the pathophysiology of their tinnitus and not to any associated comorbidities, such as sleep disturbance or diminished quality of life.

The reason individuals with tinnitus seem to be able to habituate to externally generated auditory signals and not to those signals internally generated remains unknown. One fundamental difference between the two stimuli could be represented by differences in thalamocortical activation. Real sounds presented to an ear activate bilateral auditory cortical sites, whereas tinnitus almost always results in asymmetrical activation of the auditory cortex [41]. Numerous studies that have been published concerning functional imaging (PET scans) in tinnitus patients have shown increased activity consistently in one hemisphere, primarily the left, regardless of tinnitus laterality or bilaterality [42–45].

Of interest, the pattern of reaction-time variability observed in our cohort of tinnitus patients is similar to that observed in other cohorts of subjects with asymmetrical cortical activation. In a group of patients with stroke accompanied by neglect, variability in RT was observed [46] and was likely a consequence of the asymmetrical hemisphere activation known to characterize patients with right hemisphere stroke and neglect [47,48]. In a study of healthy college students, Mennemeier et al. (personal communication) found that unequal cerebral activation (asymmetrical activation) using visual stimuli was associated with greater variability in estimating the size of sensory stimuli.

The asymmetrical activation observed in these studies seems to promote variability in performance, whether it be RT or sensory perception, by introducing a degree of neural "noise" into the system that might also interfere with the process of habituation. Neural noise resulting from asymmetrical cortical activation could also disrupt sustained attention over time. Our study documents poor sustained attention to auditory stimulation in patients with tinnitus in the absence of any deficits in responding to externally generated sounds. These results might be integrated with current findings on the central mechanisms of tinnitus if brought in line with asymmetrical cortical activation.

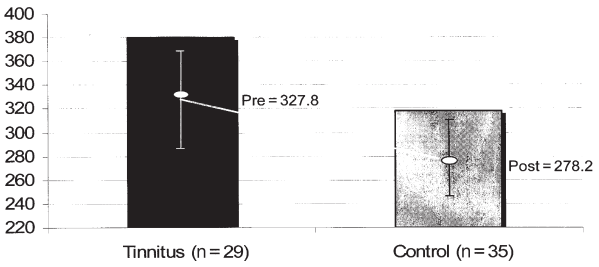


Figure 2. Results of reaction-time testing in a particular tinnitus subject before and after repetitive transcranial magnetic stimulation as compared to a series of tinnitus patients and controls. Slowest 10% response time in this patient improved, with the posttreatment results becoming similar to those of the control group in our study.

Whether interventions designed to treat tinnitus can restore symmetry and alleviate performance variability represents the next logical step in this research. One new intervention, neuronavigated low-frequency repetitive transcranial magnetic stimulation (rTMS), has been shown to exert sustained therapeutic effects on tinnitus sensation when targeting asymmetrically active areas of the primary auditory cortex [45].

Using the technique described by Kleinjung et al. [45], we recently performed rTMS guided by PET and computed tomography (CT) on a 43-year-old man with a more than 30-year history of bilateral tinnitus. Tinnitus, by report, was worse in the left ear, which correlated with 20–30% greater activation of the right primary auditory cortex versus the left on PET-CT. One week after completion of the treatment, the patient reported a 50% reduction of tinnitus using a visual analog loudness scale. Interestingly, the man likewise showed an improvement in slowest 10% RT, with the posttreatment results becoming similar to those of the control group in our study (Fig. 2; manuscript in preparation). Future work in our laboratory will focus on mechanisms involved with this apparent improvement in tinnitus sensation and performance by longitudinally studying individuals who have been treated with rTMS using tinnitus perception, PVT, and functional imagery (PET-CT).

CONCLUSION

Though no universally accepted theory of tinnitus generation exists, most believe that it is related to central nervous system dysfunction, such as thalamocortical dysrhythmia, even though peripheral injury is the inciting event. Use of the P50 auditory-evoked response amplitude and paired-stimulus paradigm revealed no impairment in arousal, with a normal ability to habituate to external auditory stimuli in the tinnitus patients as com-

pared to controls. However, a significant deficit in sustained attention occurred, as measured by the slowest responses on the PVT, suggesting a failure of cortical modulation of the thalamocortical processes related to attention. These findings were not related to sleep disturbance or tinnitus severity, suggesting that the functional deficits may be linked to the pathophysiology of the patients' tinnitus and not to any associated comorbidities. The performance variability and perhaps the inability to habituate to the internally generated sounds are hypothesized to be related to asymmetrical cortical activation that is known to characterize this condition.

ACKNOWLEDGMENT

This study was supported by NIH National Center for Research Resources Centers of Biomedical Research Excellence (COBRE) grant number RR020146.

REFERENCES

1. Mcfadden D. *Tinnitus: Facts, Theories, and Treatments*. Washington, DC: National Academy Press, 1982.
2. Jastreboff PJ, Gray WC, Gold SL. Neurophysiological approach to tinnitus patients. *Am J Otol* 17:236–240, 1996.
3. Coles R. Epidemiology of Tinnitus. In J Hazell (ed), *Tinnitus*. Edinburgh: Churchill Livingstone, 1987:46–70.
4. Kadner A, Viirre E, Wester DC, et al. Lateral inhibition in the auditory cortex: An EEG index of tinnitus? *Neuroreport* 13:443–446, 2002.
5. Muhlnickel W, Elbert T, Taub E, Flor H. Reorganization of auditory cortex in tinnitus. *Proc Natl Acad Sci U S A* 95:10340–10343, 1998.
6. Wallhausser-Franke E, Braun S, Langner G. Salicylate alters 2-DG uptake in the auditory system: A model for tinnitus? *Neuroreport* 7:1585–1588, 1996.
7. Rauschecker JP. Auditory cortical plasticity: A comparison with other sensory systems. *Trends Neurosci* 22:74–80, 1999.
8. Hallam RS, McKenna L, Shurlock L. Tinnitus impairs cognitive efficiency. *Int J Audiol* 43:218–226, 2004.
9. Nieschalk M, Hustert B, Stoll W. Auditory reaction times in patients with chronic tinnitus with normal hearing. *Am J Otol* 19:611–618, 1998.
10. Cuny C, Norena A, El Massioui F, Chery-Croze S. Reduced attention shift in response to auditory changes in subjects with tinnitus. *Audiol Neurootol* 9:294–302, 2004.
11. Bernal B, Altman NR. Auditory functional MR imaging. *AJR Am J Roentgenol* 176:1009–1015, 2001.
12. Buchwald JS, Rubinstein EH, Schwafel J, Strandburg RJ. Midlatency auditory evoked responses: Differential effects of a cholinergic agonist and antagonist. *Electroencephalogr Clin Neurophysiol* 80:303–309, 1991.
13. Erwin R, Buchwald JS. Midlatency auditory evoked responses: Differential effects of sleep in the human. *Electroencephalogr Clin Neurophysiol* 65:383–392, 1986.
14. Erwin RJ, Buchwald JS. Midlatency auditory evoked responses: Differential recovery cycle characteristics. *Electroencephalogr Clin Neurophysiol* 64:417–423, 1986.
15. Adler LE, Pachtman E, Franks RD, et al. Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. *Biol Psychiatry* 17:639–654, 1982.
16. Freedman R, Adler LE, Waldo MC, et al. Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: Comparison of medicated and drug-free patients. *Biol Psychiatry* 18:537–551, 1983.
17. Parasuraman R. The Psychobiology of Sustained Attention. In JS Warm (ed), *Sustained Attention and Human Performance*. Chichester, England: John Wiley, 1984: 61–101.
18. Posner MI. The Psychobiology of Attention. In M Gazzaniga, C Blakemore (eds), *Handbook of Psychobiology*. New York: Academic Press, 1975:441–480.
19. Sturm W, Longoni F, Fimm B, et al. Network for auditory intrinsic alertness: A PET study. *Neuropsychologia* 42: 563–568, 2004.
20. Coull JT. Neural correlates of attention and arousal: Insights from electrophysiology, functional neuroimaging and psychopharmacology. *Prog Neurobiol* 55:343–361, 1998.
21. Dinges P. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behav Res Methods* 17:652–655, 1985.
22. Folmer RL, Griest SE, Martin WH. Chronic tinnitus as phantom auditory pain. *Otolaryngol Head Neck Surg* 124:394–400, 2001.
23. Miles LE. Sleep Disorders Questionnaire. In C Guilleminault (ed), *Sleeping and Waking Disorders: Indications and Techniques*. Menlo Park, CA: Addison Wesley, 1982:383–413.
24. Boop FA, Garcia-Rill E, Dykman R, Skinner RD. The P1: Insights into attention and arousal. *Pediatr Neurosurg* 20:57–62, 1994.
25. Buchwald JS, Erwin R, Schwafel J, Tanguay P. Abnormal P1 potentials in autistic subjects. *Neurosci Abstr* 14:771, 1988.
26. Buchwald JS, Erwin RJ, Read S, et al. Midlatency auditory evoked responses: Differential abnormality of P1 in Alzheimer's disease. *Electroencephalogr Clin Neurophysiol* 74:378–384, 1989.
27. Clothier J, Scruggs JT, Gamble LJ, et al. The P1/P50 midlatency auditory evoked potential in depression. *Sleep* 21:224, 1998.
28. Rasco L, Skinner RD, Garcia-Rill E. Effect of age on sensory gating of the sleep state–dependent P1/P50 midlatency auditory evoked potential. *Sleep Res Online* 3:97–105, 2000.
29. Sahakian BJ, Morris RG, Evenden JL, et al. A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. *Brain* 111(3): 695–718, 1988.
30. Teo C, Rasco L, al-Mefty K, et al. Decreased habituation of midlatency auditory evoked responses in Parkinson's disease. *Mov Disord* 12:655–664, 1997.

31. Teo C, Rasco L, Skinner RD, Garcia-Rill E. Disinhibition of the sleep state–dependent p1 potential in Parkinson's disease—improvement after pallidotomy. *Sleep Res Online* 1:62–70, 1998.
32. Jastreboff PJ. Phantom auditory perception (tinnitus): Mechanisms of generation and perception. *Neurosci Res* 8:221–254, 1990.
33. Jeanmonod D, Magnin M, Morel A. Low-threshold calcium spike bursts in the human thalamus. Common physiopathology for sensory, motor and limbic positive symptoms. *Brain* 119(2):363–375, 1996.
34. Llinas R, Ribary U, Jeanmonod D, et al. Thalamocortical dysrhythmia: I. Functional and imaging aspects. *Thal Relat Systems* 1:237–244, 2001.
35. Fann AV, Preston MA, Bray P, et al. The P50 midlatency auditory evoked potential in patients with chronic low back pain (CLBP). *Clin Neurophysiol* 116:681–689, 2005.
36. Moller AR. Similarities between chronic pain and tinnitus. *Am J Otol* 18:577–585, 1997.
37. Hallam RS, Rachman S, Hinchcliffe R. Psychological Aspects of Tinnitus. In S Rachman (ed), *Contributions to Medical Psychology*. Oxford: Pergamon Press, 1984:31–53.
38. Mesulam MM. A cortical network for directed attention and unilateral neglect. *Ann Neurol* 10:309–325, 1981.
39. Posner MI, Dehaene S. Attentional networks. *Trends Neurosci* 17:75–79, 1994.
40. Watson RT, Valenstein E, Heilman KM. Thalamic neglect. Possible role of the medial thalamus and nucleus reticularis in behavior. *Arch Neurol* 38:501–506, 1981.
41. Lockwood AH, Salvi RJ, Burkard RF. Tinnitus. *N Engl J Med* 347:904–910, 2002.
42. Langguth B, Eichhammer P, Wiegand R, et al. Neuronavigated rTMS in a patient with chronic tinnitus. Effects of 4 weeks treatment. *Neuroreport* 14:977–980, 2003.
43. Arnold W, Bartenstein P, Oestreicher E, et al. Focal metabolic activation in the predominant left auditory cortex in patients suffering from tinnitus: A PET study with [18F]deoxyglucose. *ORL J Otorhinolaryngol Relat Spec* 58:195–199, 1996.
44. Giraud AL, Chery-Croze S, Fischer G, et al. A selective imaging of tinnitus. *Neuroreport* 10:1–5, 1999.
45. Kleinjung T, Eichhammer P, Langguth B, et al. Long-term effects of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic tinnitus. *Otolaryngol Head Neck Surg* 132:566–569, 2005.
46. Anderson B, Mennemeier M, Chatterjee A. Variability not ability: Another basis for performance decrements in neglect. *Neuropsychologia* 38:785–796, 2000.
47. Heilman KM, Watson RT, Valenstein E. Neglect and Related Disorders. In KM Heilman, E Valenstein (eds), *Clinical Neuropsychology*. New York: Oxford University Press, 1985:243–293.
48. Kinsbourne M. The cerebral basis of lateral asymmetries in attention. *Acta Psychol (Amst)* 33:193–201, 1970.