

# Alterations in Event Related Potentials (ERP) Associated with Tinnitus Distress and Attention

Wolfgang Delb · Daniel J. Strauss · Yin Fen Low ·  
Harald Seidler · A. Rheinschmitt · T. Wobrock ·  
Roberto D'Amelio

Published online: 3 October 2008

© The Author(s) 2008. This article is published with open access at Springerlink.com

**Abstract** Tinnitus related distress corresponds to different degrees of attention paid to the tinnitus. Shifting attention to a signal other than the tinnitus is therefore particularly difficult for patients with high tinnitus related distress. As attention effects on Event Related Potentials (ERP) have been shown this should be reflected in ERP measurements (N100, phase locking). In order to prove this hypothesis single sweep ERP recordings were obtained in 41 tinnitus patients as well as 10 control subjects during a period of time when attention was shifted to a tone (attended) and during a second phase (unattended) when they did not focus attention to the tone. Whereas tinnitus patients with low distress showed a significant reduction in both N100 amplitude and phase locking when comparing

the attended and unattended measurement condition a group of patients with high tinnitus related distress did not show such ERP alterations. Using single sweep ERP measurements the results of our study show, that attention in high tinnitus related distress patients is captured by their tinnitus significantly more than in low distress patients. Furthermore our results provide the basis for future neurofeedback based tinnitus therapies aiming at maximizing the ability to shift attention away from the tinnitus.

**Keywords** Tinnitus · Attention · Phase locking · Event related potentials (ERP) · N100 · N1

## Introduction

Tinnitus is an extremely frequent symptom around the world and about one-third of the population in western societies (Davis 1995; Hiller and Goebel 2007) experience tinnitus at least once in their life. Possible mechanisms for the origin of tinnitus on the cochlear and neural level have been discussed by Eggermont and Roberts (2004) as well as Zenner (1998). Nevertheless, the mechanism for the development of high and low tinnitus related distress remains unclear. According to the model by Hazell and Jastreboff (1990) the tinnitus associated signal passes from the source, e.g., the cochlea, through subcortical filters and detection stages until it is perceived and evaluated in the auditory and other cortical areas. In this processing system, there is an emotional weighting (Jastreboff 1990; Jastreboff et al. 1996) of the signal which either results in its habituation or amplification. Whereas in patients with low tinnitus related psychological impact a habituation is predominant, amplification and associated emotional and vegetative reactions are the underlying mechanism in the

---

W. Delb (✉) · A. Rheinschmitt  
ENT-Department, University of Saarland, HNO-Klinik  
Kirrbergerstr, Homburg/Saar 66421, Germany  
e-mail: hnowdel@uniklinik-saarland.de; delb@cdb-unit.de

D. J. Strauss  
Leibniz-Institute for New Materials, Saarbrücken 66111,  
Germany

D. J. Strauss · Y. F. Low  
Computational Diagnostics and Biocybernetics Unit, University  
of Applied Science, Building 90, Homburg/Saar 66421,  
Germany

H. Seidler  
Mediclin Bosenberg Hospital, St. Wendel 66606, Germany

T. Wobrock  
Department of Psychiatry und Psychotherapy, University of  
Göttingen, von-Siebold-Str. 5, Göttingen 37075, Germany

R. D'Amelio  
Department of Psychiatry, University of Saarland,  
Homburg/Saar 66421, Germany

development of a high psychological tinnitus impact. The emotional weighting depends on many factors such as a dysfunctional tinnitus related cognition or the degree of depression (Delb et al. 1999). Due to the close connection of the tinnitus and the negative emotional associations related to it, there is an attentional focus on the tinnitus. Therefore, the most effective therapeutic approaches in decompensated (high distress) tinnitus patients focus on dysfunctional emotionally biased cognitions in relation to tinnitus in order to reduce the attentional focus on the tinnitus (Andersson et al. 2005; Delb et al. 2002; Hazell and Jastreboff 1990; Kröner-Herwig et al. 1995).

Attention related amplitude changes of the N1 potential have frequently been reported in literature (Hillyard et al. 1973; Janata 2001; Näätänen et al. 1978, Näätänen 1979; Coch et al. 2005; Thornton et al. 2007; Müller et al. 2003). Differences in N1 amplitude between tinnitus and non tinnitus subjects have also been shown by Jacobson et al. (1996) and Jacobson and McCaslin (2003). They observed significantly smaller N1 amplitudes in tinnitus patients as compared to subjects without tinnitus. Also Attias et al. (1996) observed N1 amplitude as well as latency differences between tinnitus and non tinnitus patients. Norena et al. (1999) found significant amplitude differences with respect to N1–P2 amplitudes at higher stimulus intensities when comparing the tinnitus and non tinnitus ear in patients with unilateral tinnitus. It might be hypothesized that the difference in N1 amplitudes between tinnitus patients and non tinnitus patients (Jacobson and McCaslin 2003) is due to the attention tinnitus patients pay to the tinnitus which has also been discussed by Norena et al. (1999). A possible reason for that could be that during ERP measurements attention is normally neither focused on the stimulus used to measure ERP signals nor on a signal other than the stimulus. In tinnitus patients, however, according to the neurophysiological tinnitus model attention is focused to the tinnitus related signal due to its emotional load. In other words attention is to a lesser degree focused on the stimulus which results in the observed reduction in N1 amplitude in tinnitus patients as compared to non tinnitus patients (Jacobson et al. 1996; Jacobson and McCaslin 2003). Consequently as in patients with high tinnitus related distress attention is focused to the tinnitus to a higher degree as compared to patients with low distress differences in N1 amplitudes between these two groups of patients could be expected. In previous articles we (Strauss et al. 2008) as well as others (Walpurger et al. 2003) were able to demonstrate differences in N1 amplitude between tinnitus patients with high and low tinnitus related distress. We (Strauss et al. 2008) were also able to show that these amplitude differences between patients with high and low tinnitus related distress were mainly due to differences in phase locking. However, attention effects on phase locking

to the stimulus have also been shown to be one major mechanism for N1 amplitude increases due to an attention shift to the stimulus (Thornton et al. 2007; Low et al. 2007). Therefore, N1 amplitudes as well as phase locking to the stimulus in the latency range between 100 and 250 ms might be an indirect measure for the attention paid to the tinnitus which in turn is connected to tinnitus related distress.

It was the aim of the present study to find evidence that tinnitus patients with high and low tinnitus related distress differ with respect to the degree attention is captured by the tinnitus. According to the neurophysiological tinnitus model such a difference could be expected due to the fact that the tinnitus signal shows a highly emotional connotation in disabling tinnitus which is not the case in tinnitus that is associated with low distress. Selective attention is therefore much more directed to the tinnitus in patients with higher levels of distress as compared to patients who are able to cope with their tinnitus. According to the data cited above differences between tinnitus patients with high and low distress with respect to the amount of selective attention captured by the tinnitus could be objectively determined using ERP measurements. Particularly N1 amplitudes as well as phase locking are likely to be useful to demonstrate this difference (Thornton et al. 2007; Strauss et al. 2008).

## Patients and Methods

### Subjects

#### *Control Subjects*

Control subjects were student volunteers from Saarland University with normal hearing (thresholds lower than 15 dB HL in the standard frequencies of the audiogram). All subjects had no history of tinnitus, sudden hearing loss, or any other type of pathology of the ear. A total of 10 (aged 22–29 years, four females, six males) subjects entered the study.

#### *Tinnitus Patients*

About 41 consecutive tinnitus patients (29 male and 12 female) treated at the University of Saarland tinnitus clinic were enrolled in the study. Ages ranged from 22 to 66 years with a mean age of 48.6 ( $\pm 9.95$ ) years. About 35 of our patients were right handed and 6 left handed. Only patients with normal ( $\leq 15$  dB HL) hearing from 125 to 2,000 Hz were included in the study. About 26 patients in our group had a bilateral, 6 a unilateral right sided, and 9 a unilateral left sided tinnitus. According to the tinnitus questionnaire of Goebel and Hiller (Goebel and Hiller

**Table 1** Ages and results of the psychoacoustic measurements in the groups with high (2) and low (1) tinnitus related distress

	Tinnitus severity	<i>N</i>	Mean	Standard deviation	Level of significance
Age (Years)	1.00	26	48.76	10.04	$p > 0.05$
	2.00	15	48.26	10.14	
Mean hearing loss (right ear)	1.00	26	19.02	13.57	$p > 0.05$
	2.00	15	21.66	10.02	
Mean hearing loss (left ear) (dB HL)	1.00	26	17.98	7.29	$p > 0.05$
	2.00	15	21.73	8.40	
Mean threshold of uncomfortable loudness (dB HL); right ear	1.00	16	79.50	16.12	$p > 0.05$
	2.00	12	79.99	16.50	
Mean threshold of uncomfortable loudness (dB HL); left ear	1.00	17	79.52	16.15	$p > 0.05$
	2.00	11	74.25	16.33	
Beck depression inventory	1.00	24	8.67	6.83	$p < 0.01$
	2.00	14	18.50	8.34	
Tinnitus pitch (right side) (Hz)	1.00	16	6093.75	3397.15	$p > 0.05$
	2.00	8	3312.50	2701.68	
Tinnitus pitch (left side) (Hz)	1.00	18	5638.89	3170.66	$p > 0.05$
	2.00	8	3937.50	2210.97	

1998) (see below) which is a German version of the Hallam et al. (1988) tinnitus questionnaire 26 of our patients could be classified as subjects with low tinnitus related distress (main score  $<47$ ) whereas 15 of our patients exhibited a high tinnitus related distress (main score  $\geq 47$ ). When comparing patients with high and low tinnitus related distress no significant difference could be shown regarding age, hearing loss in any of the frequencies evaluated, pitch, minimal masking level using white noise, and threshold of uncomfortable loudness (Table 1).

#### Psychoacoustic Measurements

**Audiogram:** pure tone thresholds were measured at the standard frequencies between 125 and 10,000 Hz in 1 dB steps using a computer audiometer (Auritec AT900).

**Tinnitus pitch measurements:** tinnitus pitch was measured as the frequency of a pure tone of the standard audiogram corresponding most closely to the predominant pitch of the tinnitus. In order to do this, a two-alternative forced choice method was used.

**Uncomfortable loudness threshold:** the threshold of uncomfortable loudness was measured using pure tones at the standard frequencies of the audiogram.

#### Psychological Test

##### Evaluation of Tinnitus Related Distress

In order to measure the degree of distress caused by the tinnitus, the tinnitus questionnaire by Goebel and Hiller

(1998) was used. This questionnaire is a German version of the questionnaire by Hallam (Hallam et al. 1988). It consists of 52 items. Tinnitus related distress is evaluated using the main score and six subscores of the questionnaire (emotional distress, cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbances, and somatic complaints). Regarding the main score a maximum of 84 points is possible. Main score values between 0 and 46 points correspond to a low and moderate tinnitus related distress whereas values above 46 represent a high or very high tinnitus related distress.

##### Beck Depression Inventory

The German Translation of the Beck Depression Inventory (Beck and Steer 1987; Hautzinger et al. 1994) was used to estimate the degree of depression in our tinnitus patients.

##### ERP Measurements

ERPs were obtained by using a commercially available amplifier (g. tec USBamp, Guger Technologies Austria). In order to do so, we delivered three tone bursts (1 kHz, 1.3 kHz, and 1.6 kHz) at 90 dB (HL) of 40 ms duration monaurally in random order at a randomized interstimulus interval of 1–2 s (Rise/Fall time of the stimulus: 3 ms, plateau 34 ms). The probability for each of the three tones to appear was approximately 0.3. Meanwhile, the contra lateral ear was presented with music. The randomized stimulation paradigm was used to maximize (Low et al. 2007) the attention that is required to pay attention to the

stimulus and solve a task. Subjects were required to pay attention to the stimulus and press a button each time when the target tone (1.3 kHz; tone B) appeared in the first 10 min of the experiment. A sign was given to the subject after 10 min and the subjects were then instructed to ignore the stimuli and to think of something pleasant. As the subjects had to indicate that he/she realized the sign vigilance was controlled at that point in time as well as at the end of the experiment. Furthermore subjects were asked whether they had fallen asleep during the experiment. Eyes were kept closed throughout the measurements. Single sweeps, i.e., the responses to the individual tones, were recorded using electrodes placed on the left and right mastoid, the vertex (Cz), and the upper forehead (Fpz). Electrode impedances were below 5 k $\Omega$  in all measurements (filter: 1 Hz–30 Hz, sampling frequency: 512 Hz). In patients with both sided tinnitus as well as the control subjects the pure tones were applied to the right ear. In patients with one sided tinnitus the pure tones were applied to the side where the tinnitus was perceived.

#### Data Analysis and Calculation of ERP Phase Locking

##### *N1 Amplitudes*

N1 amplitudes were determined by identifying the most negative peak in the latency range between 80 and 130 ms.

##### *Calculation of ERP Phase Locking*

In the standard analysis of ERPs averages of ERP sequences are used and visually analysed. However, in this type of analysis much information is lost and it has been shown in previous publications (Kolev and Yordanova 1997; Strauss et al. 2004, 2005) that the analysis of the responses to every single sweep can expose information that is not seen in the averaged potentials. Recently time-scale coherence measures based on the complex wavelet transform have been introduced which take the non stationary nature of evoked potentials into account. This wavelet coherence increases with the correlation of the envelopes between two signals as well as if their phases show smaller variations in time. The wavelet phase coherence defined by Lachaux et al. (1999) which is relatively robust against amplitude fluctuations can be used to measure the degree of phase locking of two signals in time. Based on this phase coherence, Strauss et al. (2005) defined a measure of synchronization stability that is able to describe the degree of phase locking in a set of auditory evoked potentials obtained as single sweep measurements (Low et al. 2007; Strauss et al. 2004, 2005, 2008). Synchronization stability in the present paper thus has been calculated as described by Strauss et al. (2005) and (2008).

As in Strauss et al. (2008) we used the 6th derivative of the Gaussian function as a wavelet. Based on the results of Strauss et al. (2008) the results are exclusively shown for a scale of  $a = 40$  where the best discrimination between high and low distressed tinnitus patients was possible.

## Results

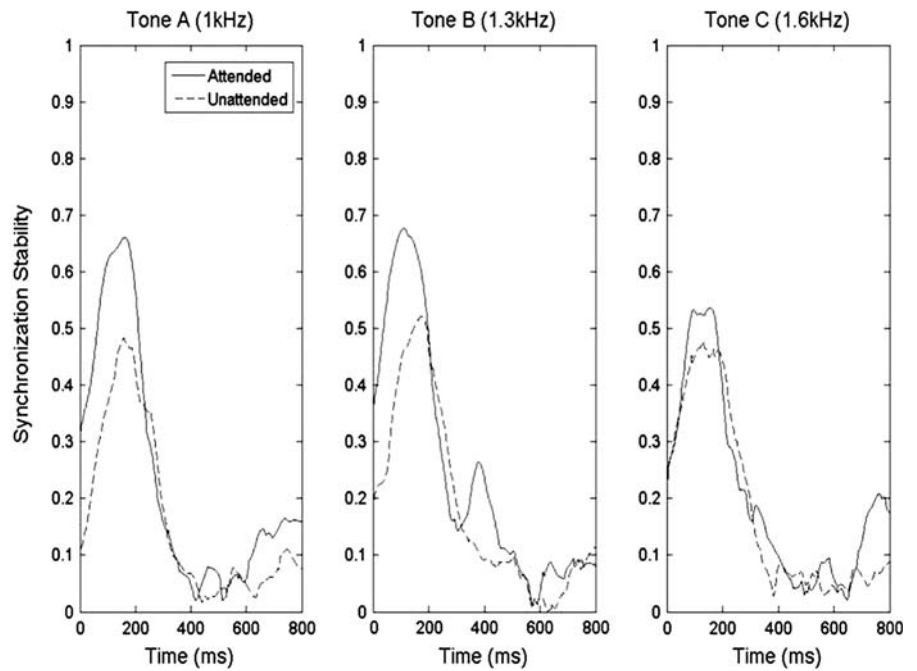
### Control Subjects

In order to evaluate the influence of attention on the synchronization stability, we measured ERP single sweeps for a measurement condition with attention directed to a target tone (“attended”), which also served as a stimulus to measure ERP and also for a measurement condition in which the subjects had to ignore the tones (“unattended”). Figure 1 shows the normalized averaged synchronization stability at  $a = 40$  of all control subjects involved in the study for both conditions (attended and unattended). It seems obvious that there is a marked and also statistically significant (Wilcoxon Test  $p < 0.05$ ) difference between the attended and unattended condition for the target tone of the experiment (1.3 kHz). These differences are associated with the time interval between 100 and 200 ms, where the waves N1 and P2 are located. In Fig. 2, the single sweep plots in both measurement conditions for an individual subject are shown. Amplitude in this figure is shown encoded by colour with light colour showing high and dark colour showing low amplitude. Each horizontal line corresponds to a single response. It seems obvious that in the attended condition, there is a prominent trace of negative amplitude around 100 ms and a trace of positive amplitude around 200 ms corresponding to waves N1 and P2 of the ERP. In the unattended condition, the trace is by far less obvious and the activity is less synchronized (higher phase jitter). As a result of this behaviour, the averaged amplitude in the unattended condition would be lower as compared to the attended condition and also the synchronization stability is lower in the unattended as compared to the attended condition.

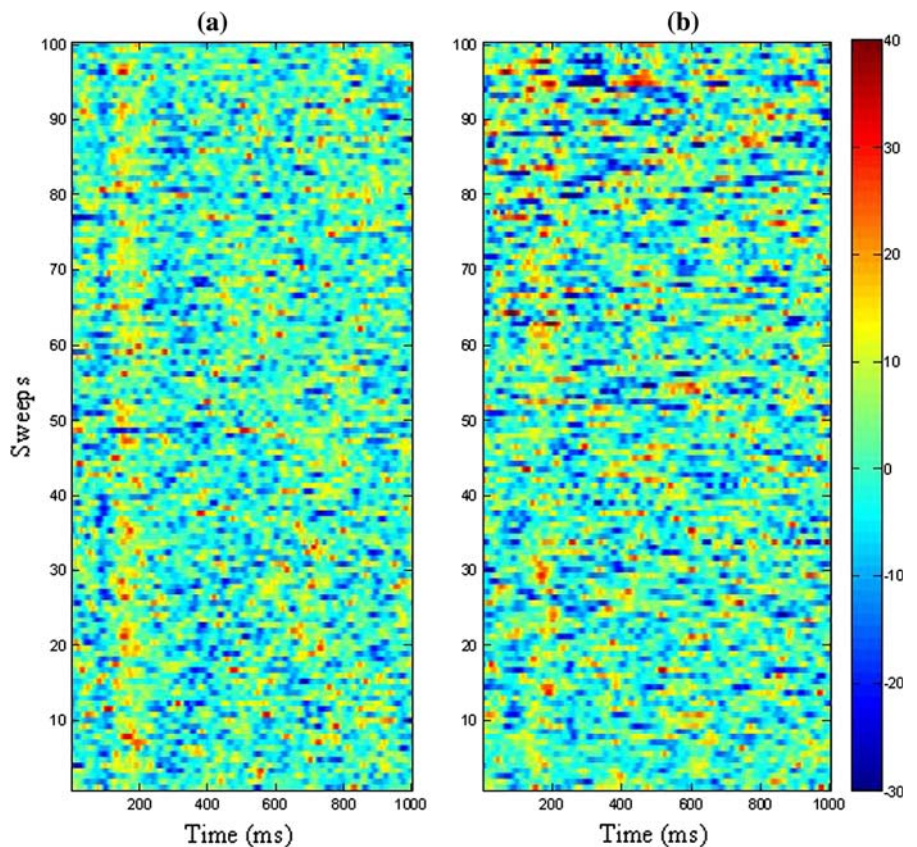
### Tinnitus Patients

Figure 3 shows N1 amplitudes in the attended (attention shifted towards the stimulus) and unattended measurement condition for patients with high and such with low tinnitus related distress as well as for control subjects. Oneway ANOVA demonstrated significant N1 amplitude differences between the three groups of patients ( $p < 0.01$ ) for the attended measurement condition. Post-hoc testing (Bonferroni procedure) showed significant N1 amplitude differences between the group of patients with high tinnitus

**Fig. 1** Synchronization stability with attention directed to the stimulus (attended) and for the measurement condition in which the subject had to ignore the stimulus (unattended). A significant difference with respect to synchronization stability can be observed in the time range up to 200 ms with the most pronounced difference in the range of 100 ms which corresponds to wave N1 of the ERP



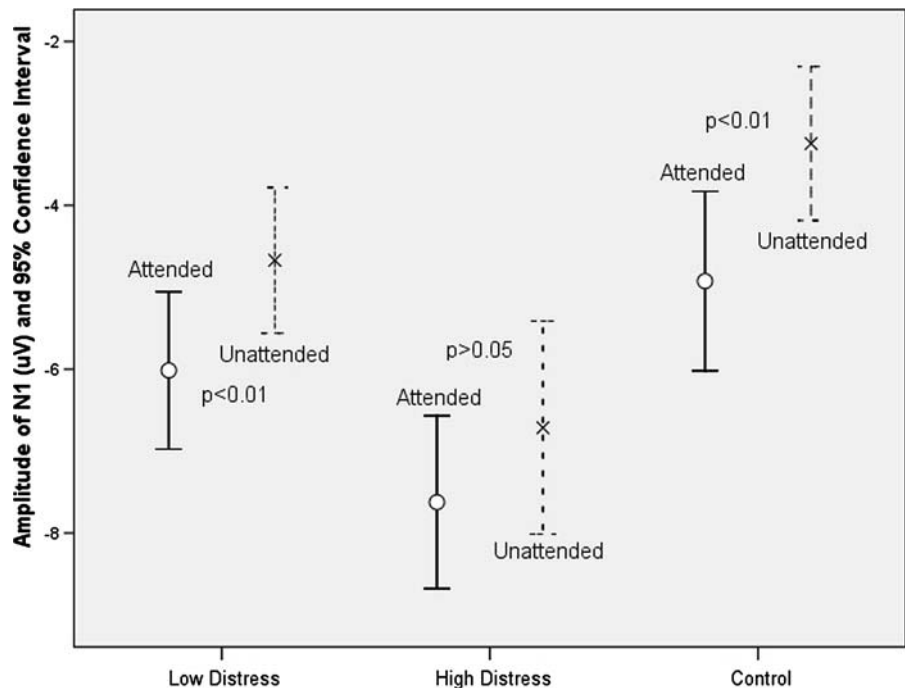
**Fig. 2** Single sweeps plot of a single patient: Each sweep corresponds to a horizontal line in the diagram. The amplitude is encoded as colour with light colour showing high and dark colours showing low amplitudes. During the time frame between 100 and 200 ms, there is a highly visible straight line in the left diagram (a, attended condition). This line corresponds to the N1 and P2 peaks of the ERP. On the right side (b) this line not as clear as a lesser degree of phase locking is present in the unattended condition



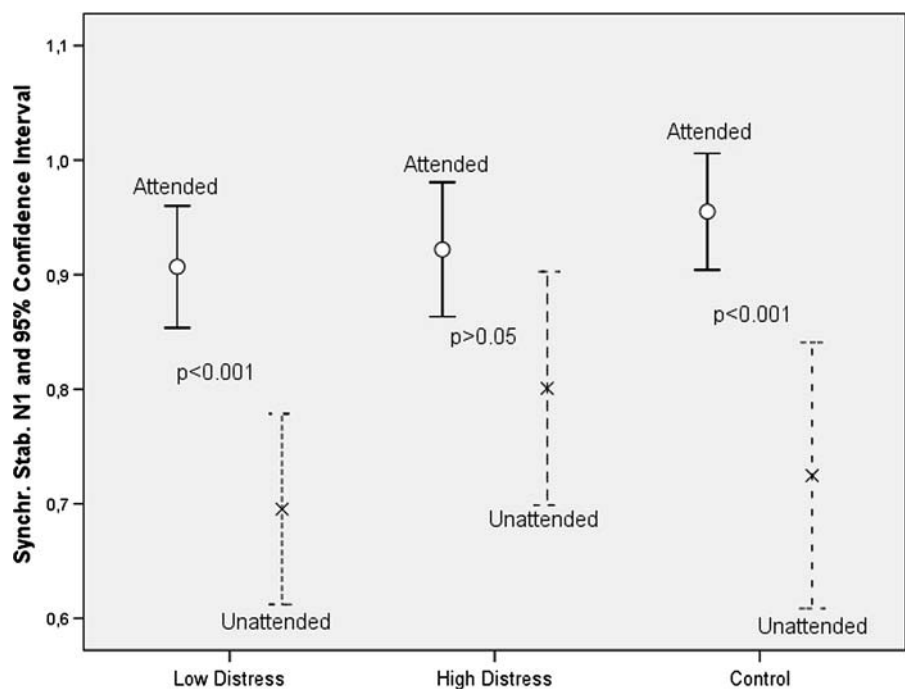
related distress and the control group whereas no significant difference was evident comparing N1 amplitudes in patients with low tinnitus related distress and the control group. In the unattended measurement condition post-hoc

testing showed significant N1 amplitude differences between patients with high and low tinnitus related distress as well as between the control group and patients with high tinnitus related distress.

**Fig. 3** Mean amplitudes ( $\mu\text{V}$ ) of N1 in the attended and unattended measurement condition in patients with low and high tinnitus related distress as well as in the control group. Shifting attention away from the stimulus results in significant amplitude change in low distress patients as well as control subjects. In patients with high tinnitus related distress such a statistically significant amplitude change could not be shown



**Fig. 4** Mean synchronization stability (normalized to the maximum amplitude in the observed latency range in the attended measurement condition) in the latency range of N1 (80 to 120 ms) in the attended and unattended measurement condition for patients with low and high tinnitus related distress as well as control subjects. Statistically significant changes of phase locking to the stimulus (synchronization stability) could be observed in the low distress group of patients as well as in our control subjects. In patients with high tinnitus related distress such a statistically significant change could not be observed

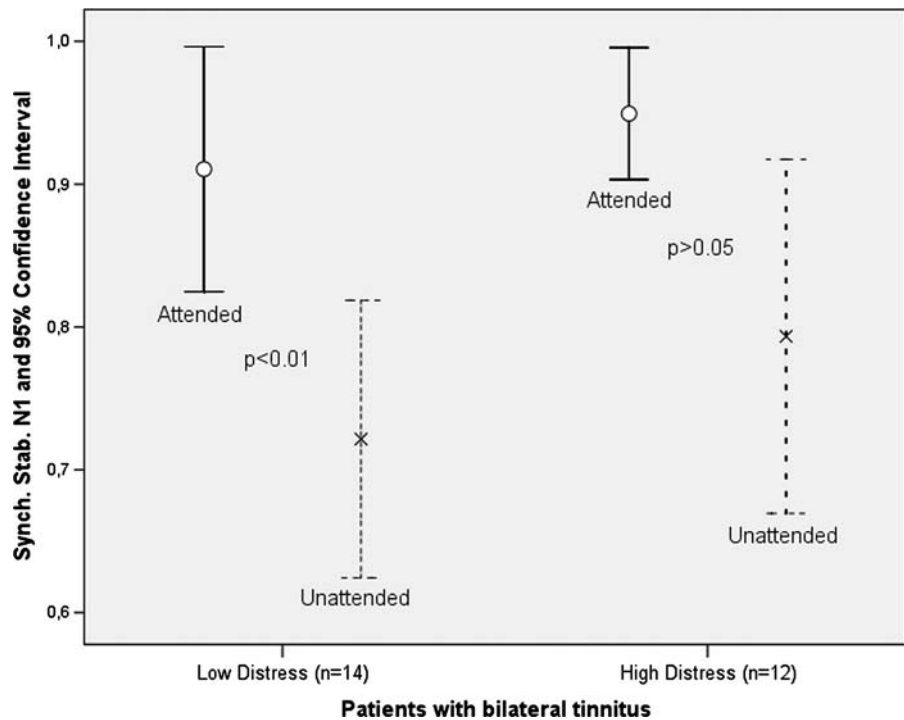


Looking at the effect of an attention shift away from the stimulus it is obvious that in the group of patients with low tinnitus related distress N1 amplitude changes significantly ( $p < 0.01$  Wilcoxon Test for paired samples) when comparing the attended (attention to the stimulus) and unattended (attention away from the stimulus) measurement condition. When looking at the group with high tinnitus related distress a significant difference between the

attended and unattended measurement condition could not be found (Wilcoxon Test for paired samples).

The synchronization stability (phase coherence in response to an auditory stimulus,  $a = 40$ ) in the latency region of N1 (80–120 ms) shows virtually the same behavior as the N1 amplitudes. In Fig. 4 the synchronization stability is shown for the latency region of N1 for the three subgroups of subjects in the attended and unattended measurement

**Fig. 5** Synchronization stability (normalized) in the latency region of N1 (80–120 ms) in a subgroup of patients with bilateral tinnitus. Also in this subgroup a attention shift away from the stimulus results in a significant (Wilcoxon Test) reduction of synchronization stability (phase locking) in low tinnitus related distress patients. In high distress tinnitus patients such a significant reduction is not observed. However, the mean reduction in synchronization stability in high distress patients with bilateral tinnitus is more pronounced than in high distress patients with unilateral tinnitus



condition. It is obvious that there is a pronounced and significant ( $p < 0.01$ , Wilcoxon Test for paired samples) reduction of synchronization stability in the N1 latency region when attention is shifted away from the pure tone stimulus. This however, is only true for patients with low tinnitus related distress. In patients with high tinnitus related distress shifting attention away from the tinnitus results in only a minor and non significant (Wilcoxon Test for Paired samples) reduction of synchronization stability.

Tinnitus patients with high and low tinnitus related distress differ with respect to the degree of depression as estimated using the Beck Depression Inventory (BDI). The correlation coefficient (Pearson) between the main score of the Goebel and Hiller (1998) questionnaire and the BDI score was 0.66 ( $p < 0.001$ ). As no patient with low tinnitus related distress exhibited a BDI score of more than 15 we focused our analysis on the subgroup of patients with high tinnitus related distress. Within this subgroup we compared patients with low and moderate BDI scores ( $< 15$ ,  $n = 6$ ) and higher BDI scores ( $\geq 16$ ;  $n = 9$ ) with respect to N1 changes induced by a shift of attention away from the stimulus. Neither N1 amplitudes nor synchronization stability between 80 and 120 ms after the stimulus showed significant changes in response to an attention shift away from the stimulus.

#### Unilateral Versus Bilateral Tinnitus

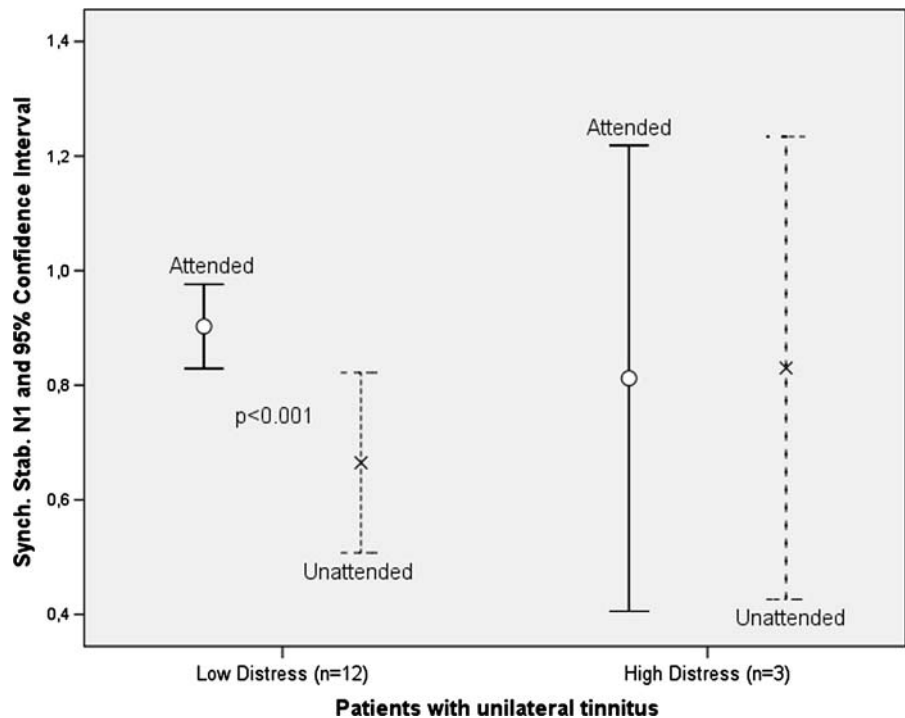
In order to demonstrate possible differences between patients with bilateral and patients with unilateral tinnitus the analysis shown above for the whole group of patients

was performed for these two groups of patients separately. Figure 5 shows the synchronization stability in the N1 latency region in patients with bilateral tinnitus. In Fig. 6 the same is shown for patients with unilateral tinnitus. In patients with unilateral tinnitus and low tinnitus related distress there is a reduction of synchronization stability as a result of shifting attention away from the stimulus in the N1 latency region. Again in the group of patients with high tinnitus related distress this reduction in amplitude is not present. In bilateral tinnitus patients with high distress the reduction in synchronization stability in response to an attention shift still does not reach statistical significance ( $p > 0.05$ , Wilcoxon Test for paired samples). However, in high distress patients there is a much higher reduction in mean synchronization stability and N1 amplitude as compared to patients with unilateral tinnitus.

#### Discussion

Our paper provides evidence that tinnitus patients with high and low tinnitus related distress show differences in their ability to shift attention. This could be shown objectively using attention effects on N1 amplitudes as well as using the phase coherence to the stimulus applied (synchronization stability, see Strauss et al. 2008). As synchronization stability is a measure that unlike N1 amplitudes can be monitored continuously it could be used in neurofeedback based tinnitus therapies aiming at optimizing the patient's ability to shift attention away from the tinnitus.

**Fig. 6** Synchronization stability (phase locking) in the latency range 80–120 ms (latency region of N1) in the subgroup of patients with unilateral tinnitus. Shifting attention away from the tinnitus results in a highly significant change in phase locking to the stimulus which is not the case when looking at highly distressed patients with unilateral tinnitus. Due to the low number of patients with high distress and unilateral tinnitus enrolled in the study no statistical test was performed for these patients. However, there is a tendency that shifting attention away from the stimulus ear which is also the ear where the tinnitus is perceived seems to be particularly difficult for these patients



In tinnitus patients with high psychological impact, a very high degree of attention is focused on the tinnitus signal in such a way that the tinnitus is always perceived. Some of these patients find it difficult to think of anything else other than their tinnitus. In contrast, in patients with low tinnitus related impact (compensated patients), the tinnitus can be “absent” (in the sense of not being perceived) for many hours during the day especially in situations where the patients focus their attention on things like work, interesting communication with other people, etc. A correlate of the described behavior of tinnitus patients with high psychological impact are the findings in recent literature (Dornhoffer et al. 2006; Stevens et al. 2007) that tinnitus patients show attentional deficits in different tasks. These authors, as well as Cuny et al. (2004), assumed a passive attention bias that resulted from permanently listening to the tinnitus. The patients in the study by Cuny et al. (2004) had to perform a task in one ear. In the other (unattended) ear, tones were applied with a deviant stimulus appearing in 30% of the cases. They observed that the task performance was better in tinnitus patients when it was performed in the tinnitus ear. They interpreted this result in such a way that the deviant stimulus to the contra lateral ear was less effective in distracting the attention from the task performed in tinnitus patients. The deficits shown in the study by Rossiter et al. (2006), who observed differences between tinnitus and control groups with regard to tasks requiring strategic controlled processing, could also be explained by the amount of attention paid to the tinnitus. In the paper by

Stevens et al. (2007), tinnitus affected the performance in an attention demanding task as well.

How can this Result be Interpreted in Light of Existing Models of Tinnitus and Selective Attention?

According to the neurophysiological tinnitus model (Jastreboff 1990) the development of a subjectively bothering tinnitus can be explained by essentially the same mechanisms as described for aversive conditioning. Here the tinnitus plays its role as a conditioned stimulus whereas tinnitus related cognitions that induce fear act as an unconditioned stimulus. By inducing plasticity in the lateral amygdala the emotional content of the tinnitus is defined and emotional as well as autonomic reactions are initiated. After the storage of the emotional content of the tinnitus, input of the amygdala via the thalamic pathways becomes more prominent and the emotional reactions to the tinnitus are present without cortical evaluation. Therefore, there should be a significant contribution of the amygdala in tinnitus pathophysiology represented in fMRI studies as well as in experimental studies. Indeed several fMRI and also experimental studies show amygdala involvement in tinnitus. De Ridder et al. (2006) injected amobarbital selectively into the anterior choroidal artery of tinnitus patients. The anterior choroidal artery is known to supply the amygdalohippocampal area. The authors report that injection of amobarbital in the anterior choroidal artery resulted in a suppression of tinnitus of 30% ipsilaterally and 70% contralaterally. Also Mirz et al. (2000) reported



amygdale activity when stimulating healthy volunteers with sounds that had been judged as being unpleasant by 10 subjects not being identical with the study subjects.

Using c-fos and 2-DG- experiments, Wallhäusser-Franke et al. (2003, 1996) and Wallhäusser-Franke (1997) were able to show that after noise trauma and the application of ototoxic drugs in animals known to result in tinnitus such a salicylate, there was a reduction in auditory nerve and cochlear nucleus activity and an elevation of auditory cortex activity. Müller et al. (2003) found a reduction in the mean spontaneous firing rate at the level of the auditory nerve after salicylate intoxication. Furthermore, Wallhäusser-Franke et al. (2003, 1996) and Wallhäusser-Franke (1997) as well as others found activity in parts of the limbic system, such as the amygdala, and the locus coeruleus. These findings are very well in accordance with clinically motivated models such as the model of Jastreboff (1990). The association between the tinnitus and the corresponding emotional reaction results in an attention shift to the tinnitus signal which is then continuously perceived as it is permanently reinforced by its emotional associations. However, tinnitus is of course not the only signal that draws the patients attention and in the real world many visual, auditory, or somatosensory signals are seeking the patient's attention. In other words the patients tinnitus is competing with sensory input of different types and attention is shifted to the stimulus with the highest stimulus salience. On the other hand the patient's attention is often shifted to a task such as reading or writing an article. In this case voluntary attention is shifted to the task that has to be performed. This attention shift is supported by top down mechanisms aiming at supporting the processing of task relevant stimuli. In other words, while attention is often captured by many stimuli that might be novel, interesting, or moving around this can to some extent be overridden by attempts to stay on task (biased competition model of selective attention, see Bishop 2008, for a review).

In the case of the experiment described in the present study the tinnitus is of varying salience being defined by its emotional load which in turn develops as described above for the neurophysiological tinnitus model. In patients with low tinnitus related distress the salience of the tinnitus is relatively low as the emotional load of this signal is also low. The opposite is the case in patients with high tinnitus related distress. However, the patients in our experiment had to perform a task (pressing a button when a particular tone appeared) and attention is tried to be shifted to the task. Depending on the emotional load of the tinnitus signal which defines its salience attention can be shifted more (low tinnitus related distress) or less (high tinnitus related distress) to the task. As the N1 wave of the ERP (Hillyard et al. 1973; Coch et al. 2005; Poghosyan and Ioannides 2008; Thornton et al. 2007) is influenced by attention this results in higher differences in N1 amplitude between the

attended and unattended stimulus conditions in patients with low tinnitus related distress as compared to patients with high distress.

In the present study, selective auditory attention had a significant effect on phase coherence to the stimulus applied. This could be shown for normal subjects as well as tinnitus patients with low tinnitus related distress. Effects of attention on phase locking to the stimulus has been shown in a previous study (Low et al. 2007) in our laboratory and has also been shown by other research groups (Kolev et al. 2001; Thornton et al. 2007). Kolev et al. (2001) described an influence of attention on event related alpha band oscillations during task processing. The main attention effects in their paper were described in the latency region above 200 ms after the stimulus. However, Thornton et al. (2007) found that the significantly increased N100 amplitude in a measurement condition with attention focused to a stimulus is accounted for by a significantly decreased latency jitter variance for the attended stimuli. Also in our study we were able to show attention effects on the amount of phase locking to the stimulus applied. In accordance with the work of Thornton et al. (2007) we observed the main effects in the latency region between 80 and 250 ms after the stimulus where the N1 and P2 waves of the ERP are typically located. Also the differences in phase locking to the stimulus (synchronization stability) between the attended and the unattended measurement condition was more pronounced and exhibited a higher level of significance as compared to the attentional effects on N1 amplitudes. This was true for patients with low tinnitus related distress. In patients with high tinnitus related distress the effect of attention on phase locking was by far less pronounced and failed to reach statistical significance. The major advantage of using the synchronization stability as described by Strauss et al. (2005) is that it can be calculated from sweep to sweep which means that it could be monitored continuously during a measurement session.

What could be a practical application of the results of the present study? Using N1 amplitudes and phase locking in the latency region between 80 and 120 ms we found objective evidence that attention in patients with high tinnitus related distress is focused more to the tinnitus as compared to patients with low distress. It therefore might be useful to apply this knowledge in neurofeedback based therapies of tinnitus aiming at maximizing the ability to shift attention away from the tinnitus. Attention training in order to shift attention away from the tinnitus is already part of frequently used cognitive- behavioural therapies of tinnitus (Delb et al. 2002). As mentioned before phase locking on the basis of single sweep measurements can be monitored continuously and is also a measure of the ability to focus attention to the stimulus which seems to be

impaired in patients with high tinnitus related distress. A neurofeedback based therapy aiming at maximizing the synchronization stability could optimize the efforts in tinnitus therapy to shift away attention from the tinnitus. First attempts in developing such a therapy have already been made in our research group (Busse et al. 2008).

**Open Access** This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

## References

- Andersson, G., Porsaeus, D., Wiklund, M., Kaldo, V., & Larsen, H. C. (2005). Treatment of tinnitus in the elderly: A controlled trial of cognitive behaviour therapy. *International Journal of Audiology*, 44, 671–675. doi:10.1080/14992020500266720.
- Attias, J., Furman, V., Shemesh, Z., & Bresloff, I. (1996). Impaired brain processing in noise-induced tinnitus patients as measured by auditory and visual event related potentials. *Ear and Hearing*, 17, 327–333. doi:10.1097/00003446-199608000-00004.
- Beck, A. T., & Steer, R. A. (1987). *Beck depression inventory—Manual*. San Antonio: The Psychological Association.
- Bishop, S. J. (2008). Neural mechanisms underlying selective attention to threat. *Annals of the New York Academy of Sciences*, 1129, 141–152. doi:10.1196/annals.1417.016.
- Busse, M., Low, Y. F., Corona-Strauss, F. I., Delb, W., & Strauss, D. J. (2008). Neurofeedback by neural correlates of auditory selective attention as possible application for tinnitus therapies. In *Proceedings of the 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. Vancouver, Canada, 20–24 August 2008.
- Coch, D., Sanders, L. D., & Neville, H. (2005). An event-related potential study of selective attention in children and adults. *Journal of Cognitive Neuroscience*, 17, 605–622. doi:10.1162/0898929053467631.
- Cuny, C., Norena, A., El Massioui, F., & Chery-Croze, S. (2004). Reduced attention shift in response to auditory changes in subjects with tinnitus. *Audiology and Neuro-Otology*, 9, 294–302. doi:10.1159/000080267.
- Davis, A. C. (1995). *Hearing in Adults*. London: Whurr.
- De Ridder, D., Fransen, H., Francois, O., Sunaert, S., Kovacs, S., & Van De Heyning, P. (2006). Amygdalohippocampal involvement in tinnitus and auditory memory. *Acta Oto-Laryngologica (Supplementum)*, 556, 50–53. doi:10.1080/03655230600895580.
- Delb, W., D'Amelio, R., Boisten, C. J., & Plinkert, P. K. (2002). Evaluation of the tinnitus retraining therapy as combined with a cognitive behavioural group therapy. *HNO*, 50, 997–1004. doi:10.1007/s00106-002-0645-5.
- Delb, W., D'Amelio, R., Schonecke, O., & Iro, H. (1999). Are there psychological or audiological parameters determining tinnitus impact? In J. Hazell (Ed.), *Proceedings of the 6th International Tinnitus Seminar* (pp. 446–451). London: The Tinnitus and Hyperacusis Centre.
- Dornhoffer, J., Danner, C., Mennemeier, M., Blake, D., & Garcia-Rill, E. (2006). Arousal and attention deficits in patients with tinnitus. *International Journal of Audiology*, 12, 9–16.
- Eggermont, J. J., & Roberts, L. E. (2004). The neuroscience of tinnitus. *Trends in Neurosciences*, 27, 676–682. doi:10.1016/j.tins.2004.08.010.
- Goebel, G., & Hiller, H. (1998). *Tinnitus-Fragebogen*. Göttingen, Bern, Toronto, Seattle, Hogrefe: Verlag für Psychologie.
- Hallam, R. S., Jakes, S. C., & Hinchcliffe, R. (1988). Cognitive variables in tinnitus annoyance. *The British Journal of Clinical Psychology*, 27, 213–222.
- Hautzinger, M., Bailer, M., Worall, H., & Keller, F. (1994). *Beck depressions-inventar (bdi) bearbeitung in deutscher Sprache. Testhandbuch*. Bern, Göttingen, Seattle: Huber.
- Hazell, J. W., & Jastreboff, P. J. (1990). Auditory mechanisms: A model for tinnitus and hearing impairment. *The Journal of Otolaryngology*, 19, 1–5.
- Hiller, W., & Goebel, G. (2007). When tinnitus loudness and annoyance are discrepant: Audiological characteristics and psychological profile. *Audiology and Neuro-Otology*, 12, 391–400. doi:10.1159/000106482.
- Hillyard, S. A., Hink, R. F., Schwent, V. L., & Picton, T. W. (1973). Electrical signs of selective attention in the human brain. *Science*, 182, 177–180. doi:10.1126/science.182.4108.177.
- Jacobson, G. P., & McCaslin, D. L. (2003). A reexamination of the long latency N1 response in patients with tinnitus. *Journal of the American Academy of Audiology*, 14, 393–400.
- Jacobson, G. P., Calder, J. A., Newman, C. W., Peterson, E. L., Wharton, J. A., & Ahmad, B. K. (1996). Electrophysiological indices of selective auditory attention in subjects with and without tinnitus. *Hearing Research*, 97, 66–74. doi:10.1016/0378-5955(96)00055-X.
- Janata, P. (2001). Brain electrical activity evoked by mental formation of auditory expectations and images. *Brain Topography*, 13, 169–193. doi:10.1023/A:1007803102254.
- Jastreboff, P. J. (1990). Phantom auditory perception (tinnitus): Mechanisms of generation and perception. *Neuroscience Research*, 8, 221–254. doi:10.1016/0168-0102(90)90031-9.
- Jastreboff, P. J., Gray, W. C., & Gold, S. L. (1996). Neurophysiological approach to tinnitus patients. *The American Journal of Otology*, 17, 236–240.
- Kolev, A., & Yordanova, J. (1997). Analysis of phase-locking is informative for studying event-related potentials. *Biological Cybernetics*, 76, 229–235. doi:10.1007/s004220050335.
- Kolev, V., Yordanova, J., Schürmann, M., & Başar, E. (2001). Increased frontal phase-locking of event-related alpha oscillations during task processing. *International Journal of Psychophysiology*, 39(2–3), 159–165.
- Kröner-Herwig, B., Hebing, G., van Rijn-Kalkmann, U., Frenzel, A., Schildowsky, G., & Esser, G. (1995). The management of chronic tinnitus—comparison of a cognitive-behavioural group training with yoga. *Journal of Psychosomatic Research*, 39, 153–165. doi:10.1016/0022-3999(94)00098-P.
- Lachaux, J. P., Rodriguez, E., Martinerie, J., & Varela, F. J. (1999). Measuring phase synchrony in brain signals. *Human Brain Mapping*, 8, 194–208. doi:10.1002/(SICI)1097-0193(1999)8:4<194::AID-HBM4>3.0.CO;2-C.
- Low, Y. F., Corona-Strauss, F. I., Adam, P., Delb, W., & Strauss, D. J. (2007). Extraction of Auditory attention correlates in single sweeps of cortical potentials by maximum entropy paradigms and its application. In *Proceeding of the 3rd International IEEE EMBS Conference on Neural Engineering* (pp. 469–472). Hawaii, USA.
- Mirz, F., Gjedde, A., Sødkilde-Jrgensen, H., & Pedersen, C. B. (2000). Functional brain imaging of tinnitus-like perception induced by aversive auditory stimuli. *Neuroreport*, 28, 633–637.
- Müller, M., Klinke, R., Arnold, W., & Oestreicher, E. (2003). Auditory nerve fibre responses to salicylate revisited. *Hearing Research*, 183, 37–43. doi:10.1016/S0378-5955(03)00217-X.
- Näätänen, R. (1979). Early selective attention effects on the evoked potential: A critical review and reinterpretation. *Biological Psychology*, 8, 81–136. doi:10.1016/0301-0511(79)90053-X.
- Näätänen, R., Gaillard, A. W. K., & Mäntylä, S. (1978). Early selective auditory attention effects on evoked potentials

- reinterpreted. *Acta Psychologica*, 42, 313–329. doi:[10.1016/0001-6918\(78\)90006-9](https://doi.org/10.1016/0001-6918(78)90006-9).
- Norena, A., Cransac, H., & Chéry-Croze, S. (1999). Towards an objectification by classification of tinnitus. *Clinical Neurophysiology*, 110, 666–675. doi:[10.1016/S1388-2457\(98\)00034-0](https://doi.org/10.1016/S1388-2457(98)00034-0).
- Poghosyan, V., & Ioannides, A. A. (2008). Attention modulates earliest responses in the primary auditory and visual cortices. *Neuron*, 12(58), 802–813. doi:[10.1016/j.neuron.2008.04.013](https://doi.org/10.1016/j.neuron.2008.04.013).
- Rossiter, S., Stevens, C., & Walker, G. (2006). Tinnitus and its effect on working memory and attention. *Journal of Speech, Language, and Hearing Research: JSLHR*, 49, 150–160.
- Stevens, C., Walker, G., Boyer, M., & Gallagher, M. (2007). Severe tinnitus and its effects on selective and divided attention. *International Journal of Audiology*, 46, 208–216. doi:[10.1080/14992020601102329](https://doi.org/10.1080/14992020601102329).
- Strauss, D. J., Delb, W., D'Amelio, R., & Falkai, P. (2005). Neural synchronization stability in the tinnitus decompensation. In *Proceeding of the 21th International IEEE EMBS Conference on Neural Engineering* (pp. 186–189). Arlington, VA, USA.
- Strauss, D. J., Delb, W., Plinkert, P. K., & Schmidt, H. (2004). Fast detection of wave V in ABR using smart single sweep analysis system. In *Proceedings of the 26th international conference of the IEEE Engineering in Medicine and Biology Society* (pp. 458–461). San Francisco, USA.
- Strauss, D. J., Delb, W., D'Amelio, R., Low, Y. F., & Falkai, P. (2008). Objective quantification of the tinnitus decompensation by synchronization measures of auditory evoked single sweeps. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 16, 74–81. doi:[10.1109/TNSRE.2007.911086](https://doi.org/10.1109/TNSRE.2007.911086).
- Thornton, A. R., Harmer, M., & Lavoie, B. A. (2007). Selective attention increases the temporal precision of the auditory N100 event-related potential. *Hearing Research*, 230, 73–79. doi:[10.1016/j.heares.2007.04.004](https://doi.org/10.1016/j.heares.2007.04.004).
- Wallhäusser-Franke, E. (1997). Salicylate evokes c-fos expression in the brain stem: Implications for tinnitus. *Neuroreport*, 8, 725–728. doi:[10.1097/00001756-199702100-00029](https://doi.org/10.1097/00001756-199702100-00029).
- Wallhäusser-Franke, E., Braun, S., & Langner, G. (1996). Salicylate alters 2-DG uptake in the auditory system: A model for tinnitus? *Neuroreport*, 7, 1585–1588. doi:[10.1097/00001756-199607080-00010](https://doi.org/10.1097/00001756-199607080-00010).
- Wallhäusser-Franke, E., Mahlke, C., Oliva, R., Braun, S., Wenz, G., & Langner, G. (2003). Expression of c-fos in auditory and non-auditory brain regions of the gerbil after manipulations that induce tinnitus. *Experimental Brain Research*, 153, 649–654. doi:[10.1007/s00221-003-1614-2](https://doi.org/10.1007/s00221-003-1614-2).
- Walpurger, V., Herbing-Lennartz, H., Denecke, H., & Pietrowsky, R. (2003). Habituation deficits in auditory event related potentials in tinnitus complainers. *Hearing Research*, 181, 57–64. doi:[10.1016/S0378-5955\(03\)00172-2](https://doi.org/10.1016/S0378-5955(03)00172-2).
- Zenner, H. P. (1998). A systematic classification of tinnitus generator mechanisms. *The International Tinnitus Journal*, 4, 109–113.