Modeling Prediction of a Generalized Habituation Deficit in Decompensated Tinnitus Sufferers

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Abstract— **The pathologic auditory sensation in decompensated tinnitus patients is accompanied by the inability to habituate even temporary to this sound. This disability might originate from simultaneous activation of brain areas for the appraisal of the stimulus valence as, e.g., the limbic system. This coactivation of limbic areas is likely to modulate the degree and persistence of selective attention assigned to the tinnitus stream, which in turn could also explain interindividual differences in tinnitus loudness perception.**

Preliminary studies demonstrate that the amount of allocated attention and the habituation deficit can be mapped to changes in auditory late evoked responses (ALRs). Utilizing a numerical model for the simulation of ALRs we were able to predict a general habituation behavior in two patient groups with different degrees of tinnitus severity.

Evaluating the instantaneous phase of simulated and measured ALRs by its von Mises concentration parameter, we verify a habituation deficit relative to the degree of decompensation and thus provide additional support for our neurofunctional model of limbic influences on neural processing of sensory information.

I. Introduction

Acoustic perceptions of tinnitus aurium are heterogeneous in their pathogenesis, tonal characteristics, as well as their individual impacts on the patient's wellbeing and daily routine. While the majority of tinnitus patients are able to cope with their tinnitus percept, about 10-15% of the patients suffer from tremendous psychosocial and psychosomatic limitations in their everyday life.

In preliminary studies we were able to demonstrate an objective correlate of a patient's distress in ALRs. We utilize the instantaneous phase of the ALR signal in the N1 component to discriminate high- and low-distress patient groups. This methodology is loosely based on the results of Hillyard et al. [1], who demonstrated the effect of focused and non-focused attention on the amplitude of the averaged ALR response. Considering single-trial responses to acoustic stimuli (sweeps) we could show that these sweeps align in their instantaneous phase during focused attention, while phase jittering increases during an inattentive state. This corresponds to different concentration parameters κ of an underlying von Mises distribution. Utilizing this methodology for analyzing ALRs in tinnitus patients we could a see an effect comparable to attentive and inattentive states in healthy subjects. The subjective distress is inversely proportional to free attention resources for processing stimuli deviant from the individual tinnitus tone. These results could explain the interindividual differences in tinnitus loudness perception.

Exposing healthy subjects to a sound-deprived environment, the majority experiences tinnitus-like acoustic phantom percepts. This effect suggests an innate physiological mechanism trying to compensate a putative hearing loss. Recent studies demonstrate an increase in spontaneous spiking in the subthalamic auditory pathway, which might account for a phantom percept. We were able to show numerically that the spike timing precision increases in a lateral inhibition network for elevated Poisson-like noisy spiking, which in turn might facilitate the selection advantage in perceptual rivalry.

However while in healthy subjects a provoked tinnitus sensation by auditory deprivation vanishes as soon as the subject is re-exposed to a normal acoustic environment the tinnitus percept persists in patients. This effect is not explicable on the base of increased spontaneous firing rate. While the aforementioned effect of increased response reliability in the N1/P2 complex of ALRs originates from thalamocortical projections [2,3,4], the effect of diminished habituation may have its origin in extrasensory brain areas that modulate neural transmission in the auditory system. We define habituation as a process of an attention-drift, away from an irrelevant target-stimulus over time during a repetitive stimulus presentation. Several studies show effects of limbic structures on cortical and subcortical tinnitus-related plastic phenomena. Plastic reorganization in the amygdala and in the thalamocortical projections can lead to forced attention capture and thus emphasize the sensation of the phantom sound in tinnitus.

We test the predictions of our model of modulated thalamocortical information transmission by comparison with experimental data. The modeling framework and experimental setup are explained in section 2.

II. Materials and Methods

A: Experimental setup: Patient groups and acoustic stimulation:

The ERP signals were collected from 18 patients of the MediClin Bosenberg Clinics with tinnitus tone average 5.11 ± 1.53kHz and moderate to severe hearing loss. Hearing ability was checked by an audiogram carried out before the experiments. The subjects were divided into two groups of tinnitus severity according to the mini-TQ12 tinnitus

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questionnaire by [5]. Decompensated group individually scored 16 or more points (grade IV); compensated group was defined by an individual score of less than 13 (grade I and II).

Ag/AgCl electrodes (Schwarzer GmbH, Germany) were attached ipsilateral to the stimulus at the corresponding mastoid (A1 or A2), common reference at the vertex (Cz), and ground at the upper forehead (Fpz). Impedances were maintained below 5kΩ in all measurements.
Subsequently, ALRs were obtained using a series of 750 1kHz pure tone transients of 40ms with an intensity level of 65 dB pe SPL and an inter-stimulus interval (ISI) of 750ms. A second set of ALRs was recorded with 40ms transients (ISI 750ms) in a frequency that fitted the tinnitus tone of each individual case.

A total of 600 sweeps, i.e., the response to an individual stimulus, free from amplitude artifacts (threshold detection of >50μV) were considered for data processing.

B: Experimental setup: Data acquisition:

The EEG data activity was collected with a 24 bit biosignal amplifier (g.USBamp, g.Tec, Austria), using a sampling frequency of 512 Hz, and a bandpass filter with low and high cutoff frequencies of 1 and 30 Hz, respectively. The intensity level was controlled by means of a programmable attenuator headphone buffer (g.PAH, g.Tec, Austria). Each sound file was generated together with its respective trigger signal. The audio channel that corresponded to the stimuli was connected to the attenuator and afterwards delivered to the subject via circumaural headphones (HDA-200, Sennheiser). The trigger channel was connected to a trigger conditioner box (g.Trigbox, g.Tec) which adapted the voltage of the trigger signal in order to be acquired by the biosignal amplifier. The acquisition-processing program and all further post-processing were achieved using tailor-made software for scientific computing (Mathworks Inc., USA).

C: Data processing: Preprocessing

After segmenting the data into single sweeps we obtain data matrices in which each row represents one trial and columns correspond to the time–sampling. We focus on the theta band ALR activity, corresponding to the N1/P2 component. To extract instantaneous phase data we generate the analytical signal

$$x_{analytic}(t) = x(t) + i[x(t) * \frac{1}{\pi t}],$$

where the imaginary part is the Hilbert transform of x(t).

D: Data processing: von Mises distribution:

The von Mises distribution is used in directional statistics for modeling circularly distributed continuous random variables (as, e.g., the instantaneous phase). It is analog to the wrapped distribution. However it has the advantage of being mathematically more tractable. In case of distributions over a (p-1) dimensional sphere $\mathbb{R}^P$, the von Mises distribution can be generalized as well, known as the von Mises Fisher distribution.

The probability density function of a von Mises distributed random variable $-\pi \leq X \leq \pi$ is given as

$$f(x|\mu, \kappa) = \frac{1}{2\pi I_0(\kappa)} e^{\kappa \cos(x-\mu)},$$

where $\mu \in [-\pi, \pi]$ and $\kappa > 0$ are mean and concentration parameter of the von Mises distribution.
$I_0(\kappa)$ is the modified Bessel function of the first kind of order 0. In this article we utilize vMF to analyze the clustering of the instantaneous phase in the time interval corresponding to the ALR N1 component. We use the mean ALR response of segments of 50 sweeps each to estimate the von Mises κ.

E: Modeling framework:

The modeling approach is based on our framework for the simulation of ALRs as presented in [6]. This framework consists of a static mean-field representation of thalmocortical feedback loops [7] coupled with an oscillatory model of an amygdalo-hippocampal comparator module based on [8] to integrate dynamic behavior. This amygdalo-hippocampal module is used to appraise stimulus valence and is able to modulate thalamocortical transmission. This modulation of the G1 loop is characterized by a sigmoid function, representing a decrease in CA1 tonic activity. The functions steepness depends on a degree of familiarity and on the influence of the amygdala on the hippocampal comparator function.
When the limbic influences prevents a quick synchronization of sensory and engrammatic CA3 inputs, the CA1 output is tonic, promoting the thalamocortical gain (G1 loop).
Integral modules in the model are depicted schematically in Fig. 1.

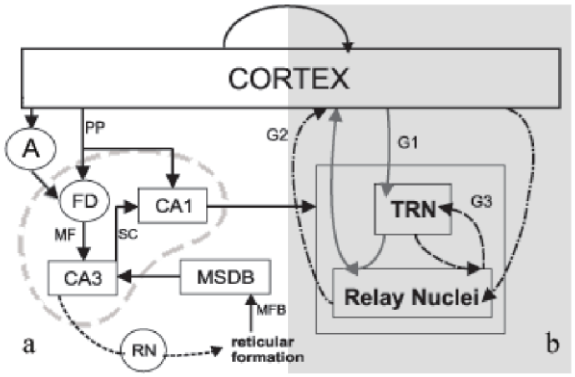

Figure 1. Schematic illustration of model parts. (grey) Thalamic module consists of Relay Nuclei (Medial Geniculate Body) and Thalamic Reticular Nucleus (TRN), interconnected with sensory cortex by three feedback gain loops (G1-G3). (white) Amygdalohippocampal module features Medial Septum/Diagonal Band of Broca (MSDB), Cornu Ammonis 1 und 3 (CA1, CA3), Fascia Dentata (FD) and Amygdala (A).

To ensure reproducibility and to account for the inter-individual anatomical variance we randomly selected the modeling parameters from a normal distribution of their physiological counterparts [9] for each run.

F: Estimation of habituation

We introduce a habituation level h as quantitative verification of the habituation trend. It is

$$h = \max\left\{0, 1 - \frac{\kappa_{\text{end}}}{\kappa_{\text{beg}}}\right\},$$

where κ_{end} is the von Mises concentration parameter of the last segment and κ_{beg} is the von Mises concentration parameter of the first segment.

III. Results

A: Modeling predictions:

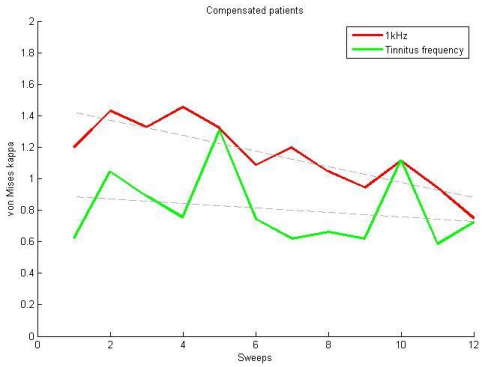

Figure 2. von Mises concentration parameter kappa over simulated sweeps for the virtual group of compensated tinnitus patients.

For compensated patients we can see a prominent decrease of the von Mises concentration parameter kappa for the insignificant 1kHz stimulation. For the stimulation in the tinnitus frequency the von Mises concentration remains constant throughout the entire simulation, indicating little to no habituation to this subjectively aversive tone.

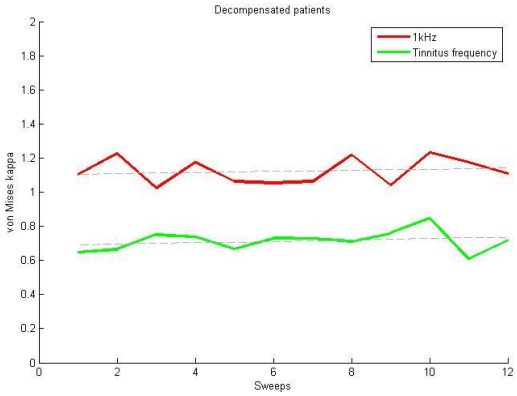

Figure 3. von Mises concentration parameter kappa over simulated sweeps for the virtual group of decompensated tinnitus patients.

In decompensated patients both von Mises concentrations remain nearly constant over all simulated stimulus presentations. Due to increased limbic influence the habituation is reduced not only for subjectively aversive tones, but also for the neutral stimulation.

B: Experimental validation:

Experimental validation of our modeling predictions was collected from 2 groups of 9 de-/compensated patients each. For the compensated patients we were able to predict the habituation behavior to both stimuli. The habituation is reduced for the subjectively aversive tinnitus tone, while being unhampered for the insignificant stimulus.

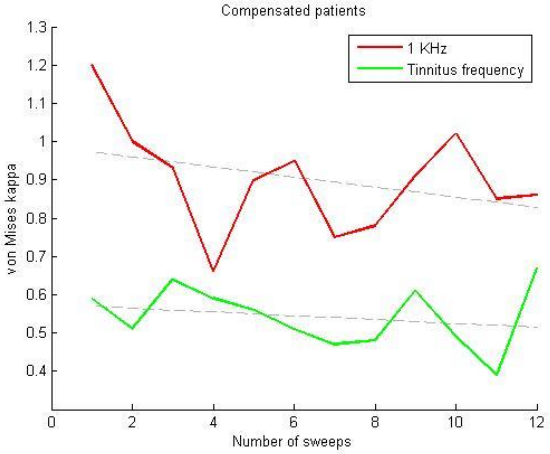

Figure 4. von Mises concentration parameter kappa over sweeps for compensated tinnitus patients. Habituation for the tinnitus frequency is significantly reduced compared to the the 1kHz stimulation

For decompensated patients we can't observe habituation at all. For the neutral stimulus as well as for the tonal reproduction of the tinnitus tone, the von Mises parameters remain constant during the entire experiment.

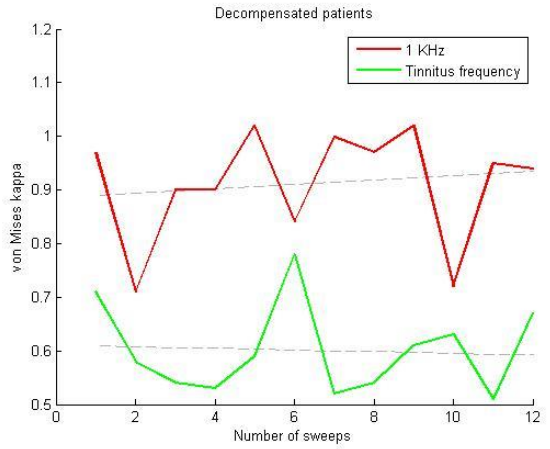

Figure 5. von Mises concentration parameter kappa over sweeps for decompensated tinnitus patients. Note that neither for the tinnitus frequency nor for the 1kHz tone the patients could habituate.

Table 1: Habituation value h for the simulated data set

Compensated patients		Decompensated patients	
h – value 1 kHz	h – value tinnitus frequency	h – value 1 kHz	h – value tinnitus frequency
0,357	0,118	0	0

Table 2: Habituation value h for the measured data set

Compensated patients		Decompensated patients	
h – value 1 kHz	h – value tinnitus frequency	h – value 1 kHz	h – value tinnitus frequency
0,188	0,121	0,028	0

IV. Discussion

Hypothesis for simulation: As outlined above we expect the origin of the habituation deficit in decompensated tinnitus patients in an overshooting reaction of limbic structures. So the habituation towards the aversive tinnitus tone should be reduced in comparison to a neutral stimulation. In terms of modeling we archive this effect by a reduction of CA1 output decrement, archiving a more or less constant modulation of the G1 gain (see [6,7] for details).
Preliminary experimental data furthermore hint towards a more generalized habituation deficit in decompensated patients, so the habituation towards the insignificant stimulus should also bind attention and thus should show less habituation.
Matching the patient group we simulated 18 runs, with modeling parameters taken randomly from a normal distribution of their physiological counterparts [9].

Experimental testing of model predictions: As seen in the results section the model was able to predict general phase behavior of ERPs in tinnitus patients for attention binding and habituation relative to their individual distress. Due to simplifications taken and physiological parameters taken from a distribution of values representing interindividual variance the model won't be able to predict the ERP time course of the individual patient. Yet being able to predict group characteristics the model might be able to extract neural mechanisms common to all tinnitus patients within a given range of individual distress. This identification of common pathologic deviations from neural signal processing in healthy subjects is unbiased and free of single-case effects or individual ERP changes resulting from co-morbidities, like, e.g. insomnia or depression.
This functional and adaptive model provides us with an archive functioning as a dynamic representation of multiscale experimental data on neural interaction in patients and animal models, bridging the gap between small-scale, but invasive animal data and large-scale, non-invasive data recorded from tinnitus patients.
Unfortunately we were confronted with high variances when estimating the von Mises concentration in experimental data. These variances might origin from the frequency dependent variation of ALRs, when stimulating with the individual tinnitus tone reproduction. The N1 component of ALRs has its origin in the activation of several frequency dependent areas in the cortex. Thus changing the frequency of the acoustic stimulation results in a dipole shift [10] and consequently in a change of the N1 morphology.

V. Conclusion

As both stimulation types were pure tones the habituation deficit towards the tinnitus tone can only be explained by an individual significance. The aversiveness of a stimulation is known to trigger limbic influence on thalamocortical information processing. As the 1kHz tone should not be of personal significance for the group of decompensated patients, we could speculate about a generalized habituation deficit underlying the tinnitus exacerbation.
The experimental results for both groups of compensated and decompensated patients bolster up the framework of our numerical model on pathologic attention binding in tinnitus aurium.

VI. Acknowledgements

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