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Modeling Limbic Influences on Habituation Deficits in Chronic Tinnitus Aurium

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Abstract—**About 93% of healthy subjects suffer from tinnitus-like symptoms when deprived of auditory stimuli, e.g., in a sound-proof chamber. This suggests an underlying physiological mechanism causing auditory sensations during absence of an external sound source. Grossberg suggested a mechanism by which hallucinations arise from mechanisms of learning, attention and volition. According to this mechanism notch-like hearing deficits are sufficient for experiencing auditory hallucinations, while their chronification is attributed to reorganization processes. In tinnitus sufferers the auditory sensation is accompanied by the inability to habituate to this endogenous sound. This disability might originate from a coactivation of brain areas that are only indirectly involved in cognitive processing such as areas belonging to the limbic system. Moreover subjective loudness of the tinnitus sensation is likely to depend on the amount of selective attention assigned to the tinnitus stream.**

Here we propose a functional model of pure–tone tinnitus in which exogenous and endogenous input into processing modules is represented as streams. We model the selection of the tinnitus stream at the subthalamic level according to its weighting. Then we propose a mechanism for the inability to habituate to this stream due to limbic coactivation and amplification by mechanisms of attentional guidance, and by the influence corticofugal projections on lower auditory processing stages. The model is able to replicate the phase stability of auditory evoked potentials as seen in tinnitus sufferers and controls

I. INTRODUCTION

Some 10 to 15% of the population in western societies suffer from auditory phantom perceptions, subsumed as tinnitus. Their tinnitus perceptions are heterogeneous in their pathogenesis and characteristics. They vary from pure-tones to complex clicking or buzzing sounds. According to Göbel and Hiller tinnitus sufferers are classified into 4 classes according to distress level [1]. Class 1 and 2 patients cope well with their tinnitus, while class 3 and 4 (1 to 3% of the population) suffer from severe social restrictions due to comorbidities like depression or insomnia. Tinnitus is often correlated with a notch-like hearing deficit. Cortical deafferentiation as caused by hearing deficits leads to a series of plastic changes spreading from the auditory cortex (AC) to subthalamic stages of the auditory pathway [2]. However, a notch-like hearing deficit is not sufficient to generate a persistent tinnitus. Rather activation of brain regions responsible for the processing of aversive stimuli, triggering reorganization in the auditory pathway appears to be required [2]. Whereas the vast majority of healthy subjects experience tinnitus-like symptoms while deprived of auditory stimuli, these symptoms become weaker with time and vanish when reexposed to a normal acoustical environment [3]. This calls for a physiological mechanism underlying the tinnitus sensation. Along this line of arguing, the pathogenic chronification of auditory phantom perceptions may thus originate in brain areas not directly involved in auditory information processing but that nevertheless influence reorganization in the auditory system. Multiple studies show effects of the limbic system on cortical and subcortical tinnitus-related plastic phenomena [4][5], especially on the inability to habituate to the tinnitus tone [6]. In the following sections we present a neurofunctional computational model incorporating the most prominent characteristics of pure–tone tinnitus. We show how plastic changes in the limbic system and the thalamocortical projections can tie down attention and enhance the sensation of the phantom sound in tinnitus patients. Additionally, we propose a mechanism by which the inability to habituate to the tinnitus tone is caused, namely by an alteration of activity in the limbic system.
Electroencephalographic studies validate the predictions of our model.

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II. MODELS AND METHODS

A. Preliminary work and motivation

We designed a model with 3 functional subunits. For this purpose we integrated a new module simulating the interaction of limbic structures with auditory areas into a framework of two already existing models that simulate early stream selection and late auditory evoked potentials by cortico–thalamic feedback dynamics (Fig. 2, block b).
According to Bregman's auditory scene analysis (ASA) [7] and the principles of Gestalt psychology the acoustic environment is subconsciously segmented into streams, each representing an external sound source and carrying a saliency value referred to as exogenous weight. The first step in the allocation of limited higher processing resources is the selection of the stream carrying the highest behavioural importance while suppressing concurrent less significant streams. The influence of such a preattentional mechanism on attentional networks has been documented in a number of studies. It was shown that the noradrenergic system has crucial impact on network reset in attentional rivalry, and on the selection of streams of high weight [8][9][10][11]. Recent human fMRI data replicated these findings, showing activation of the noradrenergic locus coeruleus (LC) in

attention and memory retrieval [12].
For modeling purposes we implemented an element for a probabilistic selection of the perceptual stream to be attended. According to the total weight of all perceptual streams, which consist of an exogenous and an endogenous weight component, the probability of selection increases with rising weight. Although the stream of highest weight is likely to be selected, the model (see Fig. 1) allows for a shift in the attended stream by attentional capturing [13].

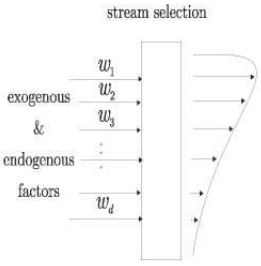

Fig. 1. Probabilistic model of early stream selection: Weighting values W_i, corresponding to attributes as stimulus background, short and long term memory as well as emotions, are assigned to every stream. It is $W_i > W_j$ for $i > j$, approximating a continuous probability distribution Γ in order to select relevant or target information based on high probability values as reflected in the dynamic stochastic distribution [14].

In our model expectation is considered to activate projections from the auditory cortex to the thalamic relay nucleus (medial geniculate body MGB) activating specific nuclei and the thalamic reticular nucleus (TRN) by increasing the gain G1 (Fig. 2, block b). The TRN plays an important role in the focussing of selective attention [15][16][17]. An increase in thalamo-cortical feedback loop activity, as implemented in the model, predicts a higher synchronization of subsequent evoked potentials, In our experimental setup we consider the rate of synchronization to be a crucial measure for attention [18].
The existing models [19], however, do not represent mechanisms of involuntary attentional shift and guidance. Therefore we added further elements to implement this feature in the model presented here. A reset of attentional networks likely produces a shift in the firing phase of the systems involved, resulting in a higher rate of synchronization for the attended perceptual stream in higher-level processing. At least for the hippocampus it is known that such a synchronization results in habituation, and that habituation is prevented by a disruption of the synchronicity in hippocampal firing [20]. In that case the stimulus cannot be matched to memory traces and is thus considered to be *new*.
Well documented is the influence of the amygdala on the firing behaviour of the hippocampus, in particular on fascia dentata (FD) [21][22]. We added this feature as a functional unit (Fig. 2, block a) to our model for the simulation of late auditory evoked responses depending on corticothalamic feedback dynamics ([19] and Fig. 2, block b).

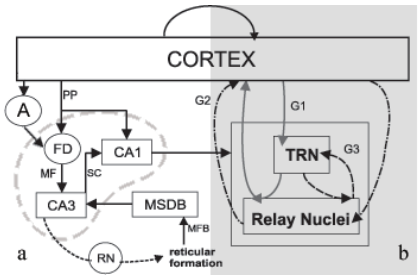

Fig. 2. Schematic overview of the presented models: The model for the simulation of cortico–thalamic interaction is depicted in block b (grey background), the additional unit is depicted in block a. Hippocampus: CA: Cornu ammonis (CA1 CA3) and FD: fascia dentata; related structures: MSDB: medial septum and diagonal band of Broca, A: amygdala, RN: Raphe nuclei, MFB: medial forebrain bundle, MF: mossy fibres, PP: perforant path, SC: Schaffer's collaterals; Thalamus: Relay nuclei - medial geniculate body (MGB) and TRN: thalamic reticular nucleus; G1-G3 are feedback loop gains for simulation purpose.

B. Modeling attentional binding due to limbic influence

The proposed model is a modular expansion of our mathematical model for the simulation of evoked responses in [19]. Our model of the hippocampal comparator function consists of four functional units located in discrete anatomical structures. The medial septum (MSDB) and FD subunits serve as modules for the formation and evolution of the neural stimulus representation by feature extraction. While MSDB activity represents the incoming perceptual stream, FD activity can be seen to represent the degree of familiarity. MSDB and FD form two inputs to the comparator subunit CA3 , which on its part is controlling the valve-element CA1. The CA1 subunit also receives input from a cortical element (entorhinal cortex) via PP. See Fig. 2, block a for a symbolic model representation. The two input streams into hippocampal CA3 are represented by three oscillating functions each, expressing theta–band potential $U(t)$

$$U(t) = A_m \cdot \frac{A_l}{1 + \exp\left(t \cdot s_n(t)\right)} \cdot sin(\omega t + \phi_1) \qquad (1)$$

and gamma band bursting U_{burst}:

$$O_{burst}(t) = \sum_{k=-\infty}^{\infty} A_b \cdot \exp(-d_{ms} t)(t - kT_0) \qquad (2)$$

$$U_{burst}(t) = \begin{cases} O_{burst} & if\ U(t)\ \geq \Theta \\ 0 & else \end{cases} \qquad (3)$$

T_0 is the base–period of the gamma–band oscillation and d_{ms} is a constant in $\mathbf{R}^+$ describing the recruiting of CA3 neurons in time. Θ is a constant in $\mathbf{R}^+$ representing the bursting threshold. Let A_m, A_b and A_l be constants in $\mathbf{R}^+$ denoting amplitudes while ϕ_1 is a constant in $\mathbf{R}^+$ representing a phase shift. $s_n(t)$ is a function in $\mathbf{R}$ acting as a slope–factor governing the evolving decrease in firing length. Habituation of the attentional allocation is archived by a synchronization

of MSDB and FD bursting. In particular, FD acts as a weakly–driven oscillator, its phasic behaviour in relation to the MSDB oscillations is expressed by Adler's equation [23]

$$\frac{d\Delta\phi}{dt} = \Delta\omega + \epsilon \cdot sin(\Delta\phi) \quad (4)$$

where ϵ represents the coupling strength. $\Delta\omega$ is the difference in oscillating frequency, $\Delta\phi$ a difference in the phase of the oscillator (FD) and the generator (MSDB). In the case of synchronization, neurons of hippocampal CA3 are prerecruited by FD and do not react to MSDB activity, thus closing the CA1 valve element. For a detailed description of algorithms underlying our model see [24]

In tinnitus sufferers the bursting behaviour of FD is modified by an independent activation of the basolateral amygdala and/or insular cortex [21][22]. Recurrent phase shifts of FD bursting prevent habituation to the perceptual stream. The perceptual stream is always considered to be unfamiliar and to be stabilized against concurrent streams [20]. Via the Raphe nuclei the MSDB directly influences the stream selection as described in I and II.A (Fig. 1). We predict a decrease in the stream reselection frequency.

A second important consequence of the increased amygdaloid activity is an enhanced long–term potentiation in the cortico–thalamic loops, simulated by an enduring increase in the G1 loop gain in Fig. 2, block b.

C. Experimental setup

In a preliminary publication, we showed a difference in the habituation behaviour of two tinnitus patients classified as grade 1 respectively 4 (TF[1]) [25] to auditory stimuli (Fig. 5), that closely resembled the habituation behaviour to aversive auditory stimuli seen in healthy controls (Fig. 3).

10 adults (4 female, 6 male) participated in this study. For all subjects normal hearing was verified by an audiogram before and immediately after the experiment. Late auditory evoked potentials (AEPs) were obtained using an acquisition system setup based on commercial devices by Guger Technologies, Austria. The subjects were told to relax during the experiment, to keep their eyes closed, to avoid movements and to ignore the presented stimuli. Auditory stimuli were pure tones of 1kHz, a duration of 40ms and a constant interstimulus interval (ISI) of 1s. We presented the stimuli at 50dB(HL) and 100dB(HL) respectively, successively with a 3 minutes interval in between. Data analysis comprised time–frequency analysis and the calculation of wavelet coherence of consecutive sweeps. See [26] for a detailed description of methods.

III. RESULTS

In addition to our results in [24], replicating in general the results of Vinogradova et al., we could confirm experimentally and in–silico a significant loss in synchronization stability of the N1–P2 component of late auditory evoked potentials (AEPs)for the habituation to a familiar stimulus (Figs. 3 and 4). This matches our experimental data found in the EEG recordings of tinnitus patients and of healthy controls exposed

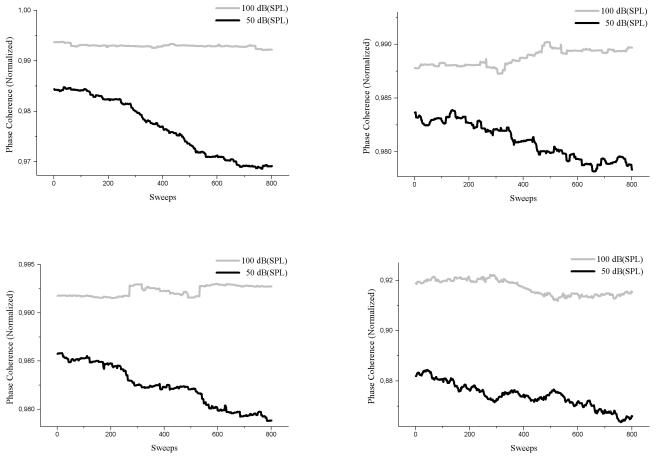

Fig. 3. Figures show representative examples of the habituation experiments for four different healthy subjects. The light grey curve depicts the normalized phase coherence over 800 stimuli for a stimulation level of 100 dB(SPL), the black curve indicates a stimulation level of 50 dB(SPL). Habituation is observed with the 50 dB(SPL) stimulus only.

to aversive auditory stimulation. Furthermore our results are in line with the findings reported by Vinogradova et al. [20].

Additionally we compared the phase–stability of late AEPs in tinnitus patients with different levels of subjective distress (class 1 and class 4 according to TF [1]). The simulation shows analogous behavior (Fig. 5).

IV. DISCUSSION AND CONCLUSION

In the experimental setup we used a model system for tinnitus distress. All subjects experienced the 100 dB(HL) stimulus as being too loud, while the same stimulus was considered to have a convenient loudness level at 50dB(HL). The stimulus presentation at 100 dB(HL) thus activates additional brain areas responsible for the processing of aversive stimuli. The amygdala is known to react even to subliminal stressors [27],

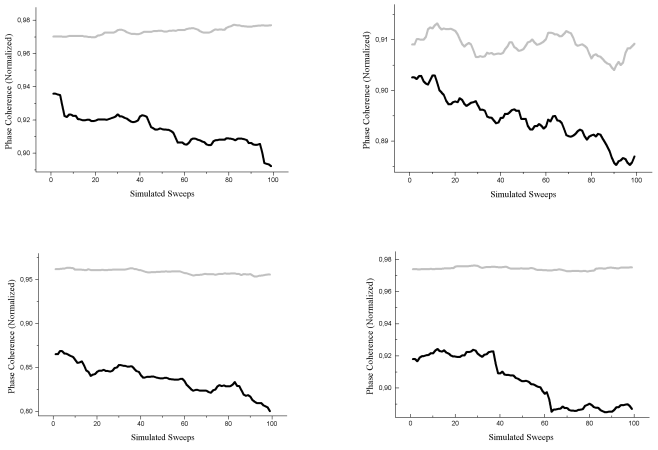

Fig. 4. Representative examples of four different simulations. The light grey curve depicts the normalized phase coherence over 100 erp–simulations for an unpleasant stimulation level, the black curve is found with a comfortable stimulation level. Time scales are not adapted to the experimental paradigm. Habituation is observed with the pleasant stimulation level only.

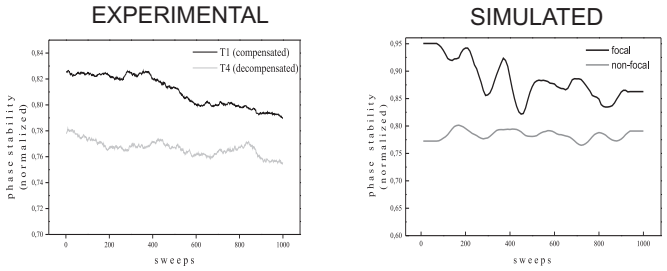

Fig. 5. Comparison of EEG–recordings in tinnitus patients (left) and simulation data (right) on phase–stability of late AEPs in tinnitus sufferers.

thereby the experimental setup is considered a valid model environment for subjective distress.

According to an investigation of the *German Tinnitus League* the loudness of a perceived tinnitus is at most some 15 dB(HL) above the individual hearing threshold in the vast majority of patients (90%). Despite this low loudness the subjective annoyance level may lead to severe psychological comorbidities even reaching the point of suicide. The level of attentional binding to the tinnitus tone may explain this phenomenon. The more attentional resources are occupied by the tinnitus tone, the more the conscious interaction with the environment is hindered. In 2007 we showed that tinnitus patients suffer from reduced attentional capacities to stimuli off their own tinnitus tone [28].

In the context of his adaptive resonance theory (ART) Grossberg presented a model of how hallucinations may arise from purely physiological mechanisms of learning, volition and attention [29]. He described a system of top–down amplification mechanisms orchestrated with inhibitory projections, so that the excitatory modulation of bottom-up information cannot produce sensations by itself. Given a damage to the inhibitory modulation the amplificating projections might then be able to evoke sensory perceptions.

Using the Vinogradova approach on hippocampus working as a comparator, we were able to simulate experimental data on attention and habituation as predicted by the theory of theta–regulated attention. The effects of attention and habituation on the N1–P2 components of late AEPs in the experimental setup were reproduced in–silico. Moreover we were able to simulate the influence of the amygdala on the consolidation of neural processing of auditory stimuli in the cortico–thalamic feedback system. The new model features mechanisms of involuntary attentional shift and guidance. So fixation and attentional binding to perceptual stream coexistent with a stressor - as in the case of tinnitus - was successfully modeled.

REFERENCES

[1] W. Goebel and W. Hiller. *Tinnitus–Fragebogen (TF). Ein Instrument zur Erfassung von Belastung und Schweregrad bei Tinnitus*. Hofgrefe, Göttingen, Germany, 1998.

[2] C. Mahlke and E. Wallhäusser-Franke. Evidence for tinnitus-related plasticity in the auditory and limbic system, demonstrated by arg3.1 and c-fos immunocytochemistry. *Hear Res.*, 195:17–34, 2004.

[3] M.F. Heller and M. Bergman. Tinnitus aurium in normally hearing persons. *Ann Otol Rhinol Laryngol.*, 62:73–83, 1953.

[4] W. Mühlnickel, T. Elbert, E. Taub, and H. Flor. Reorganization of the auditory cortex in tinnitus. In *Proc. of the National Academy of Sciences*, volume 95, pages 10340–10343, 1998.

[5] M. Mühlau, J.P. Rauschecker, E. Oestreicher, C. Gaser, M. Rttinger, A.M. Wohlschlger, F. Simon, T. Etgen, B. Conrad, and D. Sander. Structural brain changes in tinnitus. *Cereb Cortex*, 16:1283–1288, 2005.

[6] D. De Ridder, H. Fransen, O. Francois, S. Sunaert, S. Kovacs, and P. Van De Heyning. Amygdalohippocampal involvement in tinnitus and auditory memory. *Acta Otolaryngol Suppl.*, 556:50–53, 2006.

[7] A. S. Bregman. *Auditory Scene Analysis*. MIT Press, Cambridge, MA, 1999.

[8] M. Corbetta, G. Patel, and G.L. Shulman. The reorienting system of the human brain: from environment to theory of mind. *Neuron*, 58:306–324, 2008.

[9] D.S. Tait, V.J. Brown, A. Farovik, D.E. Theobald, J.W. Dalley, and T.W. Robbins. Lesions of the dorsal noradrenergic bundle impair attentional set-shifting in the rat. *Eur J Neurosci.*, 25:3719–3724, 2007.

[10] S.J. Sara. The locus coeruleus and noradrenergic modulation of cognition. *Nat Rev Neurosci*, 10:211–223, 2009.

[11] M.A. Phillips, E. Szabadi, and C.M. Bradshaw. Comparison of the effects of clonidine and yohimbine on pupillary diameter at different illumination levels. *Br J Clin Pharmacol.*, 50:65–68, 2000.

[12] V. Sterpenich, A. D'Argembeau, M. Desseilles, E. Balteau, G. Albouy, G. Vandewalle, C. Degueldre, A. Luxen, F. Collette, and P. Maquet. The locus ceruleus is involved in the successful retrieval of emotional memories in humans. *J Neurosci.*, 26:7416–7423, 2006.

[13] C.L. Folk, E.F. Ester, and K. Troemel. How to keep attention from straying: get engaged! *Psychon Bull Rev*, 16:127–132, 2009.

[14] C. Trenado, L. Haab, and D. J. Strauss. Modeling neural correlates of auditory attention in evoked potentials using corticothalamic feedback dynamics. In *In Proceedings of the 29th Conference of the IEEE Engineering in Medicine and Biology Society*, pages 4281–4284, Lyon, France, 2007.

[15] F. Crick. Function of the thalamic reticular nucleus: The searchlight hypothesis. *Proc. Natl. Acad. Sc. USA*.

[16] K. McAlonan, V.J. Brown, and E.M. Bowman. How to keep attention from straying: get engaged! *J Neurosci*, 20:8897–8901, 2000.

[17] B. Zikopoulos and H. Barbas. Prefrontal projections to the thalamic reticular nucleus form a unique circuit for attentional mechanisms. *J Neurosci*, 26:7348–7361, 2006.

[18] Y. F. Low, F. I. Corona-Strauss, P. Adam, and D. J. Strauss. Extraction of auditory attention correlates in single sweeps of cortical potentials by maximum entropy paradigms and its application. In *Proceedings of the 3st Int. IEEE EMBS Conference on Neural Engineering*, pages 469–472, Kohala Coast, HI, USA, 2007.

[19] C. Trenado, L. Haab, and D.J. Strauss. Corticothalamic feedback dynamics for neural correlates of auditory selective attention. *IEEE transactions on neural systems and rehabilitation engineering*, 17:46–52, 2009.

[20] O.S. Vinogradova. Hippocampus as comparator: role of the two input and two output systems of the hippocampus in selection and registration of information. *Hippocampus*, 11:578–598, 2001.

[21] Y. Ikegaya, H. Saito, and K. Abe. Dentate gyrus field potentials evoked by stimulation of the basolateral amygdaloid nucleus in anesthetized rats. *Brain Res.*, 718:53–60, 1996.

[22] A. Sheth, S. Berretta, N. Lange, and H. Eichenbaum. The amygdala modulates neuronal activation in the hippocampus in response to spatial novelty. *Hippocampus*, 18:169–181, 2007.

[23] R. Adler. A study of locking phenomena in oscillators. *Proceedings of the IEEE*, 61:1380–1385, 1973.

[24] L. Haab, C. Trenado, and D.J. Strauss. Neurofunctional model of limbic influences on large–scale correlates of selective attention governed by stimulus-novelty. *Biological cybernetics - submitted*, 2009.

[25] C. Trenado, L. Haab, W. Reith, and D.J. Strauss. Biocybernetics of attention and habituation neural correlates in the tinnitus decompensation. *J Neurosci Methods*, 178:237–247, 2009.

[26] Mai Mariam, W. Delb, F.I. Corona-Strauss, M. Bloching, and D.J. Strauss. Comparing the habituation of the late auditory potentials to loud and soft sounds. *J Physiol Measurement*, 30:141–153, 2009.

[27] B.J. Liddell, K.J. Brown, A.H. Kemp, M.J. Barton, P. Das, A. Peduto, E. Gordon, and L.M. Williams. A direct brainstem-amygdala-cortical 'alarm' system for subliminal signals of fear. *Neuroimage*, 24:235–243, 2004.

[28] D. J. Strauss, W. Delb, R. D'Amelio, Y. F. Low, and P. Falkai. Objective quantification of the tinnitus decompensation by synchronization measures of auditory evoked single sweeps. *IEEE Trans. on Neural Systems & Rehabilitation Engineering*, 16:74–81, 2008.

[29] S. Grossberg. How hallucinations may arise from brain mechanisms of learning, attention, and volition. *J Int Neuropsychol Soc.*, 6:583–592, 2000.