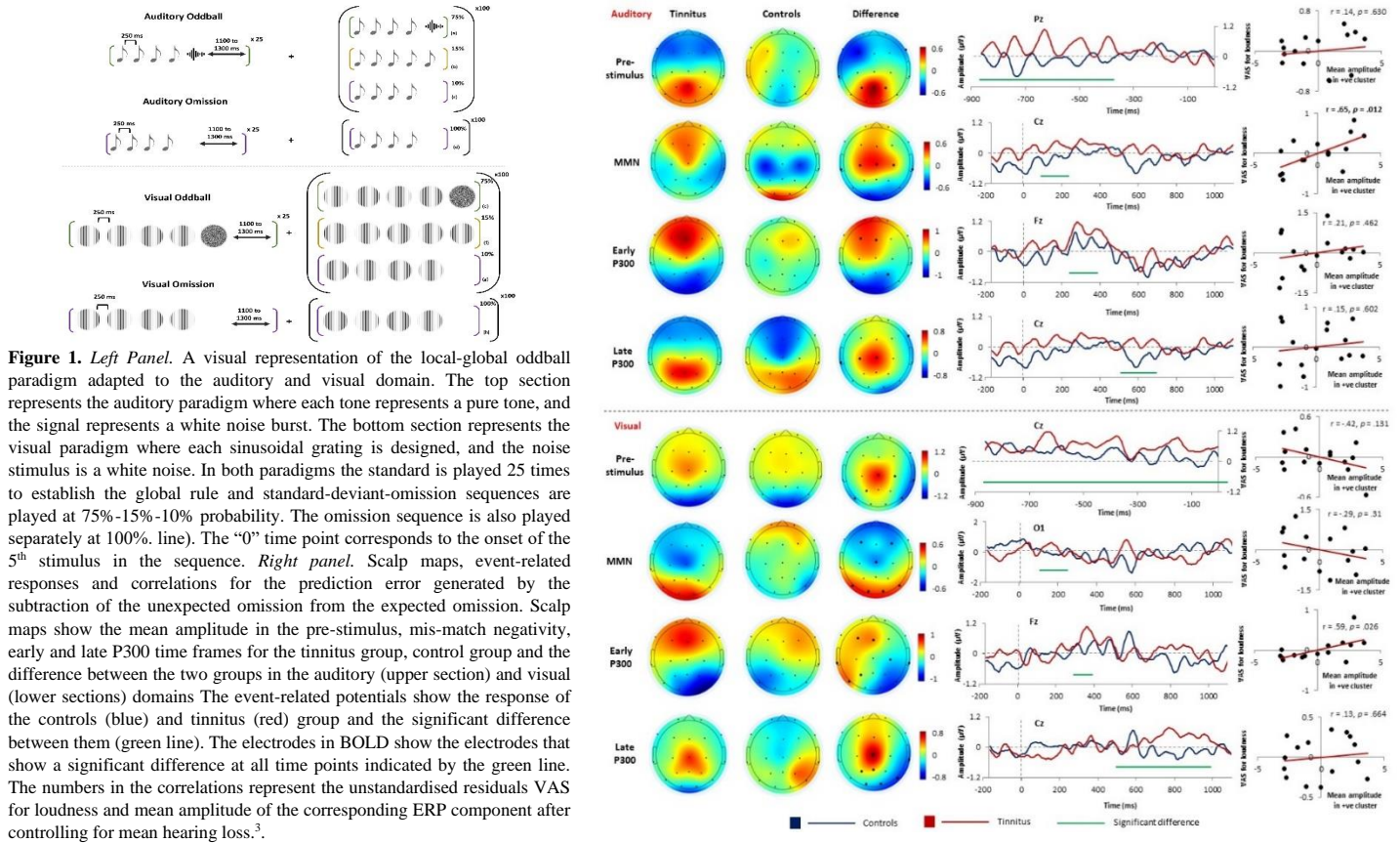


Unlocking the Potential of Predictive Coding: Pioneering Revolutionary Tinnitus Diagnostics and Treatment Approaches

Clinical auditory neuroscience is founded on the conviction that a better understanding of tinnitus related changes of brain function will significantly improve our ability to diagnose and treat tinnitus¹. Although considerable advances have been made in understanding the mechanisms of tinnitus, the clinical management of tinnitus remains largely based on a ‘trial and error’ approach². The identification and validation of a biomarker for tinnitus is thought to be the crucial step in the development of a personalized approach to the diagnosis and treatment of tinnitus. The scientific work that I introduce provides substantial evidence supporting a new theory for tinnitus that might lead to the development of a biomarker and ground-breaking research poised to pave the way for a ground-breaking treatment for tinnitus³. This fits within a larger scheme of my lab dedicated to unravelling the intricate neural mechanisms at play in tinnitus and forging innovative pathways toward its treatment (see references).



In a recent model, I explained tinnitus as a disorder of predictive coding where the brain contains an internal model of the environment⁴⁻⁶. The predictions of this model are compared with the incoming input (evidence). The weighted difference between the evidence and the prediction is the prediction error, and the weighted sum of the two is the percept which is “silence” in the absence of an external sound. In tinnitus, the evidence may be changed by bottom-up processes such as hearing loss, imbalance of excitation/inhibition of neurons in the auditory pathways, maladaptive changes in tonotopic maps etc. We demonstrated that tinnitus patients exhibit a more pronounced electrophysiological response to errors between predictions (see figure 1)³. This sensitivity to prediction errors is associated with how loud patients perceive their tinnitus, independent of the hyperacusis and the hearing loss³. More specifically, we looked at the mismatch negativity (MMN) evoked brain response. A MMN occurs across many sensory modalities in response to stimuli that differ (typically in frequency or intensity but in our experiments omitted: auditory omission) from a series of preceding stimuli (i.e., an omission oddball paradigm). In our study, the amplitude of the MMN correlated with subjectively reported tinnitus loudness. Thus, the MMN might be a biomarker for how loud tinnitus patients perceive their tinnitus. That is, people with a more pronounced electrophysiological response to a prediction error perceive a louder phantom sound. New data from my research group further confirmed that tinnitus patients demonstrated an increase in MMN amplitude for both auditory as well as visual stimuli in comparison to a control group, but that the tinnitus loudness only correlates with the amplitude of the auditory MMN (see figure 1)^{7,8}. Furthermore, an increase in amplitude and a delay in latency for the late positive evoked brain response (P300) was demonstrated in tinnitus patients for both auditory and visual oddball^{7,8}. Both the MMN and P300 are conceived as measures of prediction errors identified at respectively the sensory cortex and higher levels (i.e., frontal- parietal cortex). The P300 is thought to reflect processes involved in stimulus evaluation or categorization, in other words, whether the stimulus is behaviourally relevant or not. It is also elicited by an oddball paradigm, but reflects the positive peak after about 300 ms, rather the negative peak which represents the MMN. If the stimulus is important, it may be pushed to consciousness as represented by the P300⁹. Overall, in our seminal paper we demonstrate that MMN and the P300, can be used as (1) a biomarker for tinnitus loudness and presence, respectively as well as (2) the development of a novel treatment approach for tinnitus.

1. Clinical impact for a biomarker of tinnitus

Based on our finding, we derived a test paradigm from the most current predictive coding model of tinnitus, unpacking it in terms of depth of detail and breadth of application, and deploying it to explain wider aspects of the phenomenon than just the initial emergence of tinnitus. This development of a biomarker for tinnitus would be ground-breaking and disruptive at the same time. It

would advance patient management on a new level. By deriving a test paradigm from the here presented paper³, we can obtain an objective marker for tinnitus related to the specific pathophysiology. This may have a major impact and fill the need of the pharmaceutical and hearing tech industry for biomarkers they require to start investing in tinnitus¹⁰. In addition, due to our research we have the potential to solve the still existing uncertainty about the pathophysiological mechanisms of tinnitus generation and maintenance. As our research has identified a potential biomarker for the presence and loudness of tinnitus that could induce a paradigm shift in research, medicine, and society in how tinnitus is perceived and could lead to more awareness about the disease. Furthermore, it will lead to markedly reduce one of the patients' biggest frustrations, that they are not 'taken seriously,' that it is all in their mind, as the patients cannot prove they have tinnitus. The value of a biomarker could be enormous, including risk reduction associated with inappropriate treatment regimens or inability to detect an efficacy signal rapidly. Furthermore, the predictive coding framework has the potential to serve as the unifying theory for perceptual disorders in general by offering a means to translate findings in different sensory domains such as tinnitus, chronic pain, phantom smell and taste, visual snow syndrome, or hallucinatory experiences. It is important to note that based on this seminal paper, we have recently received funding to setup a multicenter study to validate the predictive coding framework as a method for developing a biomarker for tinnitus.

2. Clinical implications for treatment

Current attempts to suppress tinnitus are still unsuccessful because they possibly target only the evidence and/or try to modify the association between tinnitus and distress, but not change the percept or the current prediction of the brain. Based on the predictive coding paper proposed, we observe that the predisposition of tinnitus patients to produce strong predictions of their sensory environment may be leveraged towards effective learning of a new environment to generate a relevant percept. Therefore, re-training the tinnitus brain using perceptual learning of auditory stimuli outside the tinnitus frequency could (i) influence the strength of the tinnitus evidence, (ii) change the percept and its prediction from the current default.

In a recent paper, we discussed that auditory perceptual learning is the process of improving the ability of sensory systems to respond to stimuli, through experience¹¹. Auditory perceptual learning with stimulation of the locus coeruleus-noradrenaline (LC-NA) pathway in animals reliably induces long-term changes in the auditory cortex, a key area involved in the tinnitus loudness and percept^{12,13}. Previous data^{14,15} and our recent pilot data has replicated this in humans that pairing stimulating peripheral nerve stimulation with sound therapy can modify the tinnitus percept (see figure 2). The LC-NA pathway credibly promotes arousal¹⁶. Arousal improves signal-to-noise ratio by broadening frequency tuning curves and decreasing the noise floor¹⁷. This is a key component to improving frequency discrimination thresholds thereby augmenting the effects of PL¹⁸. My group revealed that the LC-NA system can be activated in humans peripherally through non-invasive transcutaneous electrical stimulation of the greater occipital nerve (NITESGON)^{19,20}. In two recent papers, we demonstrated a long-term effect of NITESGON on task-related outcomes and memory, by increasing functional connectivity from LC via the release of NA to both the amygdala and hippocampus - key areas for inducing memory stabilization and consolidation^{19,20}. Pairing auditory perceptual learning with stimulation of the locus coeruleus-noradrenaline (LC-NA) pathway in animals reliably induces long-term changes in the auditory cortex^{12,13}. The LC-NA pathway credibly promotes arousal¹⁶. Arousal improves signal-to-noise ratio by broadening frequency tuning curves and decreasing the noise floor¹⁷. This is a key component to improving frequency discrimination thresholds thereby augmenting the effects of PL¹⁸. My group revealed that the LC-NA system can be activated in humans peripherally through non-invasive transcutaneous electrical stimulation of the greater occipital (NITESGON)^{19,21,22}. We demonstrated a long-term effect of NITESGON on task-related outcomes and memory, by increasing functional connectivity from LC via the release of NA to both the amygdala and hippocampus - key areas for inducing memory stabilization and consolidation¹⁹.

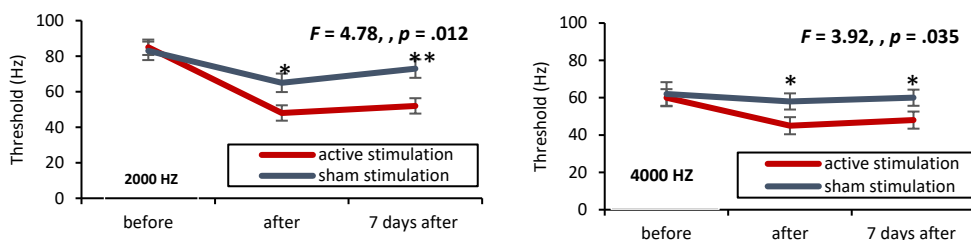


Figure 2. Longitudinal effect of placebo controlled NITESGON on auditory frequency discrimination thresholds show a significant effect for both the 2000 Hz and 4000 Hz immediately after training and 7 days after training in discrimination between the standard and the test tone. The results show improved frequency discrimination thresholds between the test tone and standard tone for the active group (n =15) in comparison to the sham group (n= 15)

By pairing NITESGON with auditory perceptual learning (APL), we can attack the key components of the predictive coding model necessary to silence tinnitus as follows – (i) Training frequencies outside the tinnitus frequency range using APL will increase plasticity of these neurons thereby activating lateral inhibition within the tinnitus frequency range as confirmed by previous research^{17,23}. This will (i) reduce the strength of the tinnitus evidence thereby decreasing tinnitus loudness; (ii) perceptual learning in a task-relevant situation will modulate top-down attention and allocate attentional resources away from the tinnitus tone thereby dissociating tinnitus loudness from distress; (iii) activation of the LC-NA pathway increases arousal which accelerates the effects¹² and long-term preservation of APL¹⁹. Thus, by pairing NITESGON with auditory perceptual learning, we will not only augment the task-relevant, attention-driven acceleration of sensory plasticity of non-tinnitus sounds and the lateral inhibition in the tinnitus frequency range but also will consolidate these changes into long-term memory. By using an active task-based bimodal stimulation design and based on our seminal paper³, we propose to reinforce the learning of reduced tinnitus loudness as the new percept which is a key step in moving the prediction of the model closer to “silence”. We have been awarded funding and are currently setting up a clinical trial as a result of this seminal paper that we present here.

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