Silencing neural symphonies with deep brain stimulation

Impact paragraph

Tinnitus is one of the major health care problems of the current era, as it poses a high burden on individuals as well as the whole society. It is expected that 2.4% of the general population suffers from the most severe degree of tinnitus, which is accompanied by a wide range of psychological symptoms such as irritability, insomnia, anxiety and depression.[1,2] Tinnitus-related costs for society are substantial, with a total estimated amount of €6.8 billion per year in the Netherlands, of which the main part is not health care related.[3] The disease specific health care costs account for 2.3% of the total health care expenditure.[3] These numbers illustrate that we are still in need of an effective therapy. So far, therapies have aimed at symptomatic relief, but fail to eliminate the tinnitus percept.[4] Deep brain stimulation (DBS) has been put forward as a potential treatment in severe tinnitus.[5] However, sufficient knowledge on neuropathophysiology of tinnitus and potential working mechanisms of DBS is still lacking, which hinders development of this therapy in severe tinnitus cases. With the preclinical studies presented in this thesis, we aimed to investigate the potential of DBS of structures within the auditory pathway to suppress tinnitus and to gain knowledge on potential neurophysiological mechanisms with regard to tinnitus and DBS. This way, we intended to help forming a solid scientific base which is needed in order to apply DBS in a clinical setting.

The main finding of this thesis is that high frequency stimulation of multiple structures within the central auditory pathway can suppress tinnitus. Additionally, our findings support the key role of the medial geniculate body (MGB) in tinnitus pathophysiology and suggest desynchronization of thalamocortical oscillations as an underlying mechanism of DBS.

Target audience

First and foremost, the work of this thesis is eventually relevant for patients and their relatives. An effective therapy for severe and refractory tinnitus is currently an unmet medical need, leading to a poor quality of life in millions of people worldwide.[4] Unfortunately, tremendous efforts in the past decades have not led to breakthroughs in the search for curative tinnitus treatments. DBS has the potential to interact with the actual core of the tinnitus network, which is a novel and therefore promising therapeutic approach. Hopefully, the findings in this thesis contribute to the development of DBS and ultimately

other types of non-invasive neuromodulation to suppress tinnitus, so that patients will benefit.
Once patients with severe, disabling tinnitus can function more independently, the general population will benefit as well. Effective treatment of severely affected tinnitus patients will be a financial relief for society, as less healthcare related costs will be made, while productivity benefits will increase as patients are able to work, consume and invest more.
Before this happens, the findings should be evaluated and incorporated by the next important target group: the academic community. The results of the behavioral studies on target choice, tinnitus suppression, side-effects, and stimulation parameters are relevant to a multi-disciplinary group of clinicians and researchers, such as neurosurgeons, ENT physicians, neurologists, audiologists and psychiatrists. In my view, a basic understanding of the complexity of a symptom such as tinnitus, as shown in this thesis, is also beneficial for general practitioners who deal on a daily basis with patients with scientifically poorly understood chronic conditions. With this background knowledge, it is possible to understand the heterogeneity of symptoms and patient presentations and can ultimately help showing compassion, which has many benefits on itself. Lastly, mechanistic findings underlying tinnitus pathophysiology and DBS effects are relevant to researchers, but also neuromodulation companies. Huge advances are being made in the field of neuromodulation. Besides optimizing DBS therapy, other non-invasive techniques are being developed that will potentially be used in auditory structures to suppress tinnitus as well. Examples are focused ultrasound or wireless magnetothermal deep brain stimulation to modulate neuronal activity.[6,7]

Innovation

The work described in this dissertation can be considered innovative in several ways. The first reason is that we used a schematic translational approach for this research line. This of course is not new on itself, but it is different compared to most previous established indications for DBS. Most indications for DBS derive from coincidental clinical findings which were subsequently directly applied in humans, often without a solid scientific base. With the evidence from our translational research line we aim to improve effectiveness and efficiency of our clinical studies. Second, we tried to shift the therapeutic focus of tinnitus. While current therapies have mostly focused on comorbidities of tinnitus in order to improve quality of life, we try and focus on the center of the problem and aim to eliminate the phantom sound by modulation of central auditory neuronal activity. Third, our findings put the MGB forward as a central key structure, a target that so far has been given just little attention in scientific tinnitus literature. As far as we are aware, we are the first to show an effect of MGB DBS on tinnitus behavior. We have shown novel findings that the MGB indeed serves as a filtering station for auditory stimulus processing, which is functioning differently in tinnitus animals. Furthermore, our explorative electrophysiological study points towards distinct roles of multiple functional classes of neurons in tinnitus pathophysiology, which need to be further investigated.

Implementation

The novel insights gained from this thesis will be implemented in various ways. Knowledge has been and will be shared in peer-reviewed international journals and during national and international conferences. On the short term, the results from the first part of this thesis lead to the clinical pilot study on MGB DBS in severe refractory tinnitus, which is currently being carried out at Maastricht UMC+. With this first-in-human study, Maastricht UMC+ is in the front line of DBS research. This clinical investigation of a novel indication for DBS impacts our international leading position in the field. With the exploratory studies of the second part of this dissertation, we encourage scientists to continue research on these electrophysiological findings. We hope that especially the MGB will be given more attention in future mechanistic and therapeutic research of tinnitus, as evidence shows promising characteristics of this structure for neuromodulative approaches. Furthermore, the clinical pilot study protocol that is presented in the third part provides a unique opportunity to record local field potentials within the human MGB. The procedure for performing these recordings will be based on the recording protocol that we developed for our preclinical study. On the longer term, well-designed studies with an adequate sample size should investigate therapeutic effects of DBS and ultimately other non-invasive neuromodulative techniques. Eventually, we should aim for individually optimized treatments, based on combined data such as each patient's symptom characteristics, neurophysiological recordings and fMRI data.

References

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