

Deep brain stimulation in tinnitus

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Impact paragraph

Tinnitus can cause a severe burden on patients and society. In the Netherlands, around 21% of the general population had tinnitus with 5.6% and 1.9% reporting it as a large and very large problem, respectively [1]. Those severely affected individuals commonly have a comorbidity of anxiety, depression, and sleep disorders. Thus, it has a considerable effect on patients' quality of life. The economical cost to society is huge as well. Annual tinnitus-related cost in the Netherlands is around €6.8 billion. Most of this cost is not akin to health care, as the productivity-related cost is more than double the health-related cost forming respectively €3702 and €1544 per patient [2]. To note, no approved treatment for tinnitus as of yet, except conservative therapy options that helps patients to cope with the distress caused by tinnitus. A substantial number of patients, however, are non-responders to these approaches. Studies reported that a large proportion of tinnitus patients are willing to spend a large sum of money or endure invasive treatments [3,4]. Therefore, there is a high demand for the development of curative therapies for tinnitus.

Understanding the disease mechanism helps to invent new therapies. Unfortunately, we have a deficit in our understanding of tinnitus' pathophysiology. In this thesis, tinnitus neuro-pathophysiology was explored. A focus was paid toward the auditory part of the thalamus, the medial geniculate body (MGB), which was suggested as a core region in the tinnitus mechanism and as a potential target for treating tinnitus with neuromodulation modalities. Deep brain stimulation (DBS) of the MGB showed its efficacy in the noise trauma-induced tinnitus model. This thesis studied the mechanism of action of MGB-DBS in this animal model through *in vivo* and immunohistochemistry approaches. Second, to translate this to humans, confirming pathological alterations in humans is a mandate. To our knowledge, no previous human postmortem study was performed on tinnitus patients. The pathological changes were studied in human postmortem materials in multiple regions including the MGB.

The findings in this thesis support the notion that MGB is a key region in tinnitus pathophysiology. Moreover, it draws more rationale for utilizing MGB-DBS for treating refractory patients and provides an explanation of its mechanism of action. Our data showed that an inhibitory feedback loop may participate in this therapeutic effect of MGB-DBS. Secondly, the findings of human postmortem studies on cellular alteration provide novel ideas for tinnitus pathophysiology. Serotonergic dysfunction as well as other cellular changes noticed in tinnitus samples needs further follow-up and may yield a scientific background for future pharmacological therapeutic options. Moreover, it stresses the need of utilizing this approach in order to understand tinnitus mechanism. As a