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Tinnitus & Cochlear Implants

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TINNITUS & COCHLEAR IMPLANTS

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1

INTRODUCTION TO THE THESIS

Tinnitus; subjective tinnitus versus objective tinnitus

Tinnitus is the perception of sound that occurs in the absence of external sound. The prevalence of tinnitus in the general population is between 5 and 43%; 10 to 30% of these patients suffer from tinnitus that lasts for more than five minutes at a time (Maes, Cima, Vlaeyen, Anteunis, & Joore, 2013; McCormack, Edmondson-Jones, Somerset, & Hall, 2016).

Tinnitus is a heterogeneous phenomenon, that is usually divided into two categories: objective tinnitus and subjective tinnitus. Objective tinnitus is caused by acoustic vibrations generated in the body reaching the ear through conduction in body tissues. An example of objective tinnitus is the sound caused by an obstructed carotid artery. Objective tinnitus is exceptional; the vast majority of patients experiences a form of subjective tinnitus. Subjective tinnitus is the percept of a meaningless sound that is not associated with a physical sound. Only the person who has this tinnitus can hear it. Subjective chronic tinnitus can be seen as a phantom sensation, similar to central neuropathic pain (Alan H. Lockwood, Salvi, Burkard, & Reyes, 2014; Møller, 2007). The sounds that patients with subjective tinnitus experience can be diverse: buzzing, whistling, sissing and rustling are the most common sounds that are mentioned. Also, the impact of subjective tinnitus on daily life is very varied. The heterogeneity of subjective tinnitus might also explain the variable responses of patients to different tinnitus treatments.

Medical conditions associate with subjective tinnitus are various (Alan H. Lockwood et al., 2014; Møller, 2007). Many of these conditions have in common that they are accompanied by peripheral hearing loss (Alan H. Lockwood et al., 2014; McCombe et al., 2001; Møller, 2007) due to:

- Noise damage to the inner ear
- Ototoxic substances: antibiotics, diuretics (furosemide), salicylate, quinine
- Disorders that affect the central nervous system: meningitis, encephalitis, strokes
- Traumatic brain damage
- Damage to the cochlear nerve: herpes infections (Ramsey Hunt), surgical damage
- Schwannomas of the cochlear nerve
- Meniere's disease

There are several hypotheses about the cause of subjective tinnitus. Most of these hypotheses state that tinnitus is caused by maladaptive plastic changes in the central auditory pathways as a consequence of peripheral hearing loss (D. M. Baguley & McFerran, 2002; James A. Henry, Roberts, Casparly, Theodoroff, & Salvi, 2014; Knipper, Van Dijk, Nunes,

Rüttiger, & Zimmermann, 2013; Knipper et al., 2020). There are two main mechanisms suggested as neural substrates of tinnitus. The first mechanism suggests an increased spontaneous firing rate of neurons in the central auditory system in response to peripheral hearing loss (Eggermont & Kral, 2016; Knipper et al., 2020; Noreña & Eggermont, 2003). A reduced activity in the affected peripheral auditory regions is thought to downregulate inhibitory central processes and this causes hyper-excitability in the central auditory system. The second possible mechanism is neural synchrony (Eggermont & Tass, 2015; Noreña & Eggermont, 2003). In normal-hearing subjects, neurons selectively respond to characteristic frequencies, and frequency tuning in the central auditory system is orderly (tonotopy). Hearing loss results in a disturbed tonotopy in the primary auditory cortex. This may cause neurons with characteristic frequencies within the region of hearing loss adopt the tuning properties to their less-affected neighbors.

In addition, there are models of tinnitus pathophysiology that propose that negative or emotional reactions to tinnitus cause the disorder to become chronic. There seems to be a relationship between tinnitus and activity in the limbic system, which includes brain regions involved in processing emotions. Additionally, some neuroimaging studies show reduced grey matter in the prefrontal cortex in tinnitus patients. This relation with the limbic system might explain why, when tinnitus symptoms are severe, it can be associated with depression, anxiety, and other psychosomatic symptoms (Knipper et al., 2020; Leaver, Seydell-Greenwald, & Rauschecker, 2016; A. H. Lockwood et al., 1998; Seki & Eggermont, 2003).

In conclusion, most hypotheses concerning tinnitus state that tinnitus perception is caused by maladaptive changes in the central auditory system as a reaction to hearing loss, and that severe tinnitus distress can be caused by maladaptive changes in the limbic system. That is why, in tinnitus treatments, both tinnitus perception as well as tinnitus related suffering should be treated.

Severity of tinnitus

Since the only person who can hear subjective tinnitus is the patient, it is difficult to measure its by auditory testing. So far, several psychoacoustic methods, such as sound matching, pitch matching, loudness matching, and minimum masking level have been studied (J. A. Henry & Meikle, 2000). These methods are effective in establishing tinnitus characteristics for research purposes and they help guide treatments such as tinnitus

masking therapy. However, these methods do not identify the impact of tinnitus in daily life. Therefore, the severity of tinnitus is often measured by assessing the consequence of tinnitus on someone's life by questionnaires that focus on quality of life, personality factors, symptoms of anxiety and depression, and social environment (Akdogan, Ozcan, Ozbek, & Dere, 2009; A. H. Lockwood et al., 1998; McCombe et al., 2001).

The severity of tinnitus is highly variable across patients. It can be only mild and cause no problems in daily life, but it can also have severe psychological and social consequences. Factors that have been shown to be associated with tinnitus, are: depression and mood disorders in 21-63% of the patients, anxiety disorders in 45%, suicidal feelings, feelings of stress and fatigue, insomnia in 25-50%, interference with work in 42% and negative effects on personal relationships in 41% (Andersson, 2002; Andersson, Freijd, Baguley, & Idrizbegovic, 2009; Holmes & Padgham, 2009; Stouffer & Tyler, 1990; Tyler & Baker, 1983; Zöger, Svedlund, & Holgers, 2001).

Tinnitus treatments

Unfortunately, there is still not a cure for tinnitus. That is why the current treatments generally focus on reducing the symptoms and consequences of the tinnitus. The treatments for tinnitus can be divided into two main categories. The first category aims to decrease the tinnitus and its related central nervous (over)activity. The second category aims to decrease the tinnitus related annoyance and the influence of the tinnitus on functioning in daily life (D. M. Baguley & McFerran, 2002).

Hearing aids

Hearing aids belong to the first category of treatments. Since most of the hypotheses state that tinnitus is caused by maladaptive plastic changes in the central auditory pathways resulting from peripheral hearing loss, devices that ameliorate the hearing loss can also help to decrease the tinnitus. Hearing aids amplify and modulate sound for people with hearing loss, to improve hearing. In addition, hearing aids can suppress the need of the central nervous system to compensate for the hearing loss with (over) activity. Several studies on the treatment of tinnitus with hearing aids have been carried out (Hoare, Edmondson-Jones, Sereda, Akeroyd, & Hall, 2014; Sereda, Hoare, Nicholson, Smith, & Hall, 2015). These studies show that there is limited evidence that hearing aids can effectively reduce tinnitus. However, some patients benefit from the treatment with hearing aids and no adverse effects have been reported with this kind of treatment. Thus,

nowadays hearing aids, combined with education and advice on tinnitus, are the most common therapy for patients suffering from both tinnitus and hearing loss (Hoare et al., 2014; Sereda et al., 2015).

Medication

Examples of medication that have been studied to treat tinnitus are: cortisone, vasodilators, benzodiazepines, lidocaine, spasmolytic drugs, anti-convulsants, antidepressants and extract from Ginkgo biloba. Unfortunately, in the majority of patients, none of the drugs were able to provide long-term significant reduction of tinnitus, when compared to placebo. For this reason, in both Europe and North America there are no drugs licensed for the treatment of tinnitus (Baldo, Doree, Molin, McFerran, & Cecco, 2012; Bauer C.A. & Brozoski T.J., 2006; Figueiredo, Langguth, Mello de Oliveira, & Aparecida de Azevedo, 2008; C. EL Hoekstra, Rynja, van Zanten, & Rovers, 2011; Jayarajan & Coles, 1993; Simpson, Gilbert, & Davies, 1999). Most medicines that were examined aim to decrease the tinnitus and the tinnitus-related central nervous (over)activity and thus also fall into the first category of tinnitus treatments.

Cognitive Behavioral Therapy

Cognitive Behavioral Therapy (CBT) aims to reduce tinnitus handicap, i.e. the degree of influence tinnitus has on daily life activities; this thus falls into the second category of tinnitus treatments. CBT treatments for tinnitus have repeatedly been shown to be effective in reducing tinnitus distress. These treatments are based on the concept that the -initially neutral- tinnitus signal receives an 'alarm' value through classical conditioning. This negative tinnitus value hinders the process of habituation. There are different kind of CBT treatments, but all are aimed at reducing negative thoughts, emotions, and behaviours resulting from tinnitus. Most of the current CBT approaches in tinnitus treatment contain third wave CBT interventions, such as acceptance and commitment therapy (ACT) and mindfulness (Andersson, 2002; Cima, van Breukelen, & Vlaeyen, 2018; Fuller et al., 2020; Jastreboff, 2011; Martinez -Devesa, Perera, Theodoulou, & Waddell, 2010).

Other treatments for tinnitus

Other possible treatment options for tinnitus that have been studied are: hyperbaric oxygen therapy, transcranial magnetic stimulation, music therapy, reflexology, hypnotherapy, mindfulness and acupuncture (C. E. L. Hoekstra, Versnel, Neggers, F., & Van Zanten, 2012; Meng, Liu, Zheng, & Phillips, 2011). However, there is insufficient evidence that any of these can significantly reduce tinnitus.

Tinnitus in cochlear implant candidates

Since tinnitus is associated with hearing loss, this also is characteristic of cochlear implant (CI) candidates, i.e. patients with severe sensorineural hearing loss. Previous research has described a prevalence of tinnitus in cochlear implant candidates ranging from 66 to 86%, with a mean prevalence of 80%. However, only 17 to 35% of these patients reported severe tinnitus (Andersson et al., 2009; David M Baguley, 2010; Kompis et al., 2012; Quaranta, Wagstaff, & Baguley, 2004).

The psychological and social consequences of tinnitus have not been extensively studied in populations with CI patients. Until now, only few studies investigated the effect of tinnitus on feelings of anxiety and depression in this population. According to these studies feelings of anxiety and depression often improve after cochlear implantation (Mo, Harris, & Lindbæk, 2002; Olze et al., 2011; Bruggeman et al., 2017). After cochlear implantation, tinnitus seldom causes anxiety (14%) or depression (5%), but when there is a high postoperative tinnitus handicap, feelings of anxiety and depression are common (Andersson et al., 2009; Olze et al., 2011).

Cochlear implantation as a tinnitus treatment

Many studies have shown that the suppression of tinnitus is a co-occurring effect of cochlear implantation. The first report of subjective tinnitus being suppressed by a cochlear implant was published by House in 1976 (House & Brackmann, 2008). Later, several studies confirmed these results, showing that suppression of tinnitus occurs in 15 to 95% of the cases (Akdogan et al., 2009; Bovo, Ciorba, & Martini, 2011; Kompis et al., 2012; Pan et al., 2009; Quaranta, Fernandez-Vega, D'Elia, Filippo, & Quaranta, 2008; Quaranta et al., 2004; Rubinstein, Tyler, Johnson, & Brown, 2003; Van De Heyning et al., 2008). However, some cochlear implant patients have reported an exacerbation (1 to 10%) or even the onset (0 to 23,5%) of tinnitus after implantation (Akdogan et al., 2009; David M Baguley, 2010; Bovo et al., 2011; Kompis et al., 2012; Quaranta et al., 2008, 2004).

Objective and outline of this thesis

Objective

Since previous studies describe a positive effect of cochlear implantation on tinnitus in the majority of cochlear implant recipients, this thesis aims to obtain more insight into the number of patients that might benefit from cochlear implantation in the population of patients with severe bilateral sensorineural hearing loss. We tried to clarify the preoperative factors that can predict the outcome of cochlear implantation on tinnitus. We also explored single electrode stimulation strategies to reduce tinnitus perception and at furthermore we tried to measure central nervous system changes associated with tinnitus reduction in cochlear implant recipients.

Outline

Chapter 2 is a review of current knowledge concerning cochlear implantation and tinnitus.

Chapter 3 describes a retrospective questionnaire study that aims to address the prevalence of tinnitus in cochlear implant patients and the changes after cochlear implantation with respect to tinnitus, tinnitus handicap, and anxiety or depression.

Chapter 4 describes a study, based on the retrospective questionnaire study, which aims to create prognostic models, using binary logistic regression analyses to predict positive or negative changes in tinnitus after cochlear implantation.

Chapter 5 is a continuation of the studies in chapters 2 and 3 and describes a prospective questionnaire study. The aim of this study is to determine the effects of cochlear implantation on tinnitus and explore which factors can influence the effect of cochlear implantation on it.

Chapter 6 describes a parametric study to test the simplest possible method for electrical stimulation via a cochlear implant, where just a single electrode was activated. Potentially, such a mode of stimulation could be combined with strategies in which the remaining electrodes were used for speech perception. The purpose of this study was to investigate whether single-electrode stimulation could reduce the loudness of tinnitus. The stimulation electrode, stimulation rate, and stimulation amplitude were varied, to seek for an optimal suppression method.

Chapter 7 describes a study that investigated the influence of a cochlear implant on the neural activity in tinnitus-related brain areas by making labelled water (H_2^{15}O) PET scans. The scans were made before and after switching the cochlear implant on and off, to examine correspondences with the subjective tinnitus experience of the patients.

REFERENCES

- Akdogan, O., Ozcan, I., Ozbek, C., & Dere, H. (2009). Tinnitus after cochlear implantation. *Auris Nasus Larynx*. <https://doi.org/10.1016/j.anl.2008.04.005>
- Andersson, G. (2002). Psychological aspects of tinnitus and the application of cognitive-behavioral therapy. *Clinical Psychology Review*. [https://doi.org/10.1016/S0272-7358\(01\)00124-6](https://doi.org/10.1016/S0272-7358(01)00124-6)
- Andersson, G., Freijd, A., Baguley, D. M., & Idrizbegovic, E. (2009). Tinnitus Distress, Anxiety, Depression, and Hearing Problems among Cochlear Implant Patients with Tinnitus. *Journal of the American Academy of Audiology*. <https://doi.org/10.3766/jaaa.20.5.5>
- Baguley, D. M., & McFerran, D. J. (2002). Current perspectives on tinnitus. *Archives of Disease in Childhood*. <https://doi.org/10.1136/ad.86.3.141>
- Baguley, David M. (2010). New Insights into Tinnitus in Cochlear Implant Recipients. *Cochlear Implants International*. <https://doi.org/10.1179/146701010x12726366068616>
- Baldo, P., Doree, C., Molin, P., McFerran, D., & Cecco, S. (2012). Antidepressants for patients with tinnitus. [Review][Update of Cochrane Database Syst Rev. 2006;(4):CD003853; PMID: 17054188]. *Cochrane Database of Systematic Reviews (Online)*. <https://doi.org/http://dx.doi.org/10.1002/14651858.CD003853.pub3>
- Bovo, R., Ciorba, A., & Martini, A. (2011). Tinnitus and cochlear implants. *Auris Nasus Larynx*. <https://doi.org/10.1016/j.anl.2010.05.003>
- Bauer C.A. & Brozoski T.J., (2006). Effect of gabapentin on the sensation and impact of tinnitus. *Laryngoscope*. <https://doi.org/10.1097/01.MLG.0000216812.65206.CD>
- Cima, R. F. F., van Breukelen, G., & Vlaeyen, J. W. S. (2018). Tinnitus-related fear: Mediating the effects of a cognitive behavioural specialised tinnitus treatment. *Hearing Research*. <https://doi.org/10.1016/j.heares.2017.10.003>
- Eggermont, J. J., & Kral, A. (2016). Somatic memory and gain increase as preconditions for tinnitus: Insights from congenital deafness. *Hearing Research*. <https://doi.org/10.1016/j.heares.2015.12.018>
- Eggermont, J. J., & Tass, P. A. (2015). Maladaptive neural synchrony in tinnitus: Origin and restoration. *Frontiers in Neurology*. <https://doi.org/10.3389/fneur.2015.00029>
- Figueiredo, R. R., Langguth, B., Mello de Oliveira, P., & Aparecida de Azevedo, A. (2008). Tinnitus treatment with memantine. *Otolaryngology - Head and Neck Surgery*. <https://doi.org/10.1016/j.otohns.2007.11.027>
- Fuller, T., Cima, R., Langguth, B., Mazurek, B., Vlaeyen, J. W. S., & Hoare, D. J. (2020). Cognitive behavioural therapy for tinnitus. *Cochrane Database of Systematic Reviews*. <https://doi.org/10.1002/14651858.CD012614.pub2>
- Henry, J. A., & Meikle, M. B. (2000). Psychoacoustic measures of tinnitus. *Journal of the American Academy of Audiology*.

- Henry, James A., Roberts, L. E., Caspary, D. M., Theodoroff, S. M., & Salvi, R. J. (2014). Underlying mechanisms of tinnitus: Review and clinical implications. *Journal of the American Academy of Audiology*. <https://doi.org/10.3766/jaaa.25.1.2>
- Hoare, D. J., Edmondson-Jones, M., Sereda, M., Akeroyd, M. A., & Hall, D. (2014). Amplification with hearing aids for patients with tinnitus and co-existing hearing loss. *Cochrane Database of Systematic Reviews*. <https://doi.org/10.1002/14651858.CD010151.pub2>
- Hoekstra, C. E. L., Versnel, H., Neggers, S. F. W., F., N. M. E., & Van Zanten, G. A. (2012). Effectiveness of bilateral repetitive transcranial magnetic stimulation in patients with chronic tinnitus [poster presentation abstract]. In *Tinnitus: The Art and Science of Innovation: Sixth International Conference on Tinnitus, Bruges, Belgium. June 13-16, 2012*.
- Hoekstra, C. EL, Rynja, S. P., van Zanten, G. A., & Rovers, M. M. (2011). Anticonvulsants for tinnitus. *Cochrane Database of Systematic Reviews*. <https://doi.org/10.1002/14651858.cd007960.pub2>
- Holmes, S., & Padgham, N. D. (2009). Review paper: More than ringing in the ears: A review of tinnitus and its psychosocial impact. *Journal of Clinical Nursing*. <https://doi.org/10.1111/j.1365-2702.2009.02909.x>
- House, J. W., & Brackmann, D. E. (2008). Tinnitus: Surgical Treatment. In *Tinnitus*. <https://doi.org/10.1002/9780470720974.ch12>
- Jastreboff, P. J. (2011). Tinnitus retraining therapy. In *Textbook of Tinnitus*. https://doi.org/10.1007/978-1-60761-145-5_73
- Jayarajan, V., & Coles, R. (1993). Treatment of tinnitus with frusemide. *Journal of Audiological Medicine*.
- Knipper, M., Van Dijk, P., Nunes, I., Rüttiger, L., & Zimmermann, U. (2013). Advances in the neurobiology of hearing disorders: Recent developments regarding the basis of tinnitus and hyperacusis. *Progress in Neurobiology*. <https://doi.org/10.1016/j.pneurobio.2013.08.002>
- Knipper, M., van Dijk, P., Schulze, H., Mazurek, B., Krauss, P., Scheper, V., ... Rüttiger, L. (2020). The neural bases of tinnitus: lessons from deafness and cochlear implants. *Journal of Neuroscience*. <https://doi.org/10.1523/JNEUROSCI.1314-19.2020>
- Kompis, M., Pelizzone, M., Dillier, N., Allum, J., Demin, N., & Senn, P. (2012). Tinnitus before and 6 months after cochlear implantation. *Audiology and Neurotology*. <https://doi.org/10.1159/000335126>
- Leaver, A. M., Seydell-Greenwald, A., & Rauschecker, J. P. (2016). Auditory-limbic interactions in chronic tinnitus: Challenges for neuroimaging research. *Hearing Research*. <https://doi.org/10.1016/j.heares.2015.08.005>
- Lockwood, A. H., Salvi, R. J., Coad, M. L., Towsley, M. L., Wack, D. S., & Murphy, B. W. (1998). The functional neuroanatomy of tinnitus: Evidence for limbic system links and neural plasticity. *Neurology*. <https://doi.org/10.1212/WNL.50.1.114>
- Lockwood, Alan H., Salvi, R. J., Burkard, R. F., & Reyes, S. A. (2014). The functional anatomy of

- tinnitus. *The Journal of the Acoustical Society of America*. <https://doi.org/10.1121/1.4744112>
- Maes, I. H. L., Cima, R. F. F., Vlaeyen, J. W., Anteunis, L. J. C., & Joore, M. A. (2013). Tinnitus: A cost study. *Ear and Hearing*. <https://doi.org/10.1097/AUD.0b013e31827d113a>
- Martinez -Devesa, P., Perera, R., Theodoulou, M., & Waddell, A. (2010). Cognitive behavioural therapy for tinnitus (Review). *The Cochrane Collaboration*. <https://doi.org/10.1002/14651858.CD005233.pub3.www.cochranelibrary.com>
- McCombe, A., Baguley, D., Coles, R., McKenna, L., McKinney, C., & Windle-Taylor, P. (2001). Guidelines for the grading of tinnitus severity: The results of a working group commissioned by the British Association of Otolaryngologists, Head and Neck Surgeons, 1999. *Clinical Otolaryngology and Allied Sciences*. <https://doi.org/10.1046/j.1365-2273.2001.00490.x>
- McCormack, A., Edmondson-Jones, M., Somerset, S., & Hall, D. (2016). A systematic review of the reporting of tinnitus prevalence and severity. *Hearing Research*. <https://doi.org/10.1016/j.heares.2016.05.009>
- Meng, Z., Liu, S., Zheng, Y., & Phillips, J. S. (2011). Repetitive transcranial magnetic stimulation for tinnitus [Systematic Review]. *The Cochrane Collaboration*. <https://doi.org/10.1002/14651858.CD007946.pub2.Copyright>
- Mo, B., Harris, S., & Lindbæk, M. (2002). Tinnitus in cochlear implant patients - A comparison with other hearing-impaired patients. *International Journal of Audiology*. <https://doi.org/10.3109/14992020209056073>
- Møller, A. R. (2007). Tinnitus: presence and future. *Progress in Brain Research*. [https://doi.org/10.1016/S0079-6123\(07\)66001-4](https://doi.org/10.1016/S0079-6123(07)66001-4)
- Noreña, A. J., & Eggermont, J. J. (2003). Changes in spontaneous neural activity immediately after an acoustic trauma: Implications for neural correlates of tinnitus. *Hearing Research*. [https://doi.org/10.1016/S0378-5955\(03\)00225-9](https://doi.org/10.1016/S0378-5955(03)00225-9)
- Olze, H., Szczepek, A. J., Haupt, H., Förster, U., Zirke, N., Gräbel, S., & Mazurek, B. (2011). Cochlear implantation has a positive influence on quality of life, tinnitus, and psychological comorbidity. *Laryngoscope*. <https://doi.org/10.1002/lary.22145>
- Brüggemann, P., Szczepek, A. J., Klee, K., Gräbel, S., Mazurek, B., Olze, H. (2017). In patients undergoing cochlear implantation, psychological burden affects tinnitus and the overall outcome of auditory rehabilitation. *Frontiers in Human Neuroscience*.
- Pan, T., Tyler, R. S., Ji, H., Coelho, C., Gehringer, A. K., & Gogel, S. A. (2009). Changes in the tinnitus handicap questionnaire after cochlear implantation. *American Journal of Audiology*. [https://doi.org/10.1044/1059-0889\(2009/07-0042\)](https://doi.org/10.1044/1059-0889(2009/07-0042))
- Quaranta, N., Fernandez-Vega, S., D'Elia, C., Filipo, R., & Quaranta, A. (2008). The effect of unilateral multichannel cochlear implant on bilaterally perceived tinnitus. *Acta Oto-Laryngologica*. <https://doi.org/10.1080/00016480701387173>
- Quaranta, N., Wagstaff, S., & Baguley, D. M. (2004). Tinnitus and cochlear implantation.

- International Journal of Audiology*. <https://doi.org/10.1080/14992020400050033>
- Rubinstein, J. T., Tyler, R. S., Johnson, A., & Brown, C. J. (2003). Electrical suppression of tinnitus with high-rate pulse trains. *Otology and Neurotology*. <https://doi.org/10.1097/00129492-200305000-00021>
- Seki, S., & Eggermont, J. J. (2003). Changes in spontaneous firing rate and neural synchrony in cat primary auditory cortex after localized tone-induced hearing loss. *Hearing Research*. [https://doi.org/10.1016/S0378-5955\(03\)00074-1](https://doi.org/10.1016/S0378-5955(03)00074-1)
- Sereda, M., Hoare, D. J., Nicholson, R., Smith, S., & Hall, D. A. (2015). Consensus on hearing aid candidature and fitting for mild hearing loss, with and without tinnitus: Delphi review. *Ear and Hearing*. <https://doi.org/10.1097/AUD.0000000000000140>
- Simpson, J. J., Gilbert, A. M., & Davies, W. E. (1999). Is lamotrigine an effective treatment for tinnitus? In *Proceedings of the Sixth International Tinnitus Seminar, Cambridge UK. September 5th-9th 1999*.
- Stouffer, J. L., & Tyler, R. S. (1990). Characterization of Tinnitus by Tinnitus Patients. *Journal of Speech and Hearing Disorders*. <https://doi.org/10.1044/jshd.5503.439>
- Tyler, R. S., & Baker, L. J. (1983). Difficulties Experienced by Tinnitus Sufferers. *Journal of Speech and Hearing Disorders*. <https://doi.org/10.1044/jshd.4802.150>
- Van De Heyning, P., Vermeire, K., Diebl, M., Nopp, P., Anderson, I., & De Ridder, D. (2008). Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation. *Annals of Otology, Rhinology and Laryngology*. <https://doi.org/10.1177/000348940811700903>
- Zöger, S., Svedlund, J., & Holgers, K. M. (2001). Psychiatric disorders in tinnitus patients without severe hearing impairment: 24 month follow-up of patients at an audiological clinic. *International Journal of Audiology*. <https://doi.org/10.3109/00206090109073108>

2

COCHLEAR IMPLANTS & TINNITUS

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CASE

A 74-year old man visited our outpatient clinic. His main complaint was a severe hearing loss in both ears. He wondered whether he might benefit from cochlear implantation. His hearing loss started at the age of 5 years, and was progressive in subsequent years. The hearing loss is familial, with 50% of the family members on his father's side affected. Besides hearing loss, the man had complaints of tinnitus and vertigo. This man used hearing aids for many years, but the aids were no longer sufficient for his amount of hearing loss. Also, did the hearing aids have no effect on his tinnitus.

ENT examination revealed a normal aspect of the eardrums, with air-filled middle ears. Tone audiometry showed a severe sensorineural hearing loss with thresholds at 85-100dB in the right ear and 100-110dB in the left ear. The best speech discrimination score was 10% on the right side and 0% on the left ear. A CT showed a pneumatised mastoid and a normal aspect of the inner ear structures on both sides. The tinnitus and hearing handicap were further assessed with questionnaires: Tinnitus Handicap Inventory, THI=10; Tinnitus Handicap Questionnaire, THQ=12; Abbreviated Profile of Hearing Aid Benefit, APHAB=96. These scores reflect a mild tinnitus handicap and a severe hearing impairment.

Cochlear implantation was performed in the left ear. After an auditory rehabilitation program, the patient was satisfied with the result. The speech discrimination score had improved to 68%. In addition, the patient mentioned that his tinnitus had considerably reduced. Questionnaire outcomes were now: THI=6, THQ=12, APHAB=37.

This case illustrates common findings in cochlear implantations. Before implantations, hearing loss is severe and tinnitus is often mildly to moderately invalidating. After cochlear implantations both speech understanding and tinnitus improve. This improvement in speech discrimination is clearly reflected in the corresponding questionnaire score. Improvements in tinnitus are not always apparent in questionnaires.

INTRODUCTION

Tinnitus is a common symptom in cochlear implant candidates. After implantation, many recipients experience a reduction of the tinnitus. The first report of subjective tinnitus being suppressed by a cochlear implant was published by House in 1976 (House, Berliner, & Crary, 1976). After that, several studies have confirmed these results (table 1). These studies also report that cochlear implantation can have negative influence on tinnitus. Nevertheless, the predominantly positive effect of cochlear implantation on tinnitus has initiated clinical trials in which the primary purpose of implantation is the suppression of tinnitus. Understanding the effects of cochlear implantation on tinnitus may open new venues for tinnitus treatment. In addition, an insight in the positive and negative effects of cochlear implantation on tinnitus may contribute to our understanding of the mechanisms of tinnitus generation. The purpose of the present chapter is to give a brief overview of the research in the area of cochlear implants and tinnitus considering the effect of cochlear implantation on tinnitus, factors predicting successful tinnitus reduction, the role of strategies for electrical stimulation and neurophysiological insights gained from neuroimaging studies.

Tinnitus in cochlear implant candidates

The prevalence of tinnitus in the general population is 8-35%. It is known that this prevalence becomes higher in the population of people with hearing loss (Coles, 1984; Shargorodsky, Curhan, & Farwell, 2010). Cochlear implantation is considered in subjects suffering from a profound sensorineural hearing loss. The prevalence of tinnitus in cochlear implant candidates ranges from 52-100% (Baguley & Atlas, 2007; Kim et al., 2013; Klooster, Arnold, Hofman, & Van Dijk, 2015; Kompis et al., 2012; Quaranta, Fernandez-Vega, D'Elia, Filipo, & Quaranta, 2008).

The high prevalence of tinnitus in the population of cochlear implant candidates is consistent with a prevailing hypothesis on the origin of tinnitus that suggests it arises as a response of the central auditory system to peripheral hearing loss (Berliner, Shelton, Hitselberger, & Luxford, 1992; Roberts et al., 2010; Silverstein, 1976; Tyler, 1984). Peripheral hearing loss results in a decrease of afferent input to the brainstem. This may result in a change of spontaneous neural activity, which is believed to potentially cause tinnitus (Eggermont & Komiya, 2000; Eggermont & Roberts, 2004; Kaltenbach, 2000; Kiang, Moxon, & Levine, 1970; Møller, 2003; Preece, Tyler, & Noble, 2003; Wang, Salvi, & Powers, 1996).

Table 1: effect of cochlear implantation on tinnitus in patients with bilateral severe hearing loss						
Study	Number of patients	Effect on tinnitus			Tinnitus deterioration	Tinnitus onset
		Tinnitus disappeared	Tinnitus improved	Unchanged tinnitus		
Tyler and Kelsey (1990)	42		34 (81%)	7 (17%)		
McKerrow et al. (1991)	6	5 (83%)		1 (17%)		
Souliere et al. (1992)	28		20 (71%)	8 (29%)		
Gibson (1992)	41		25 (61%)	16 (39%)		
Tyler (1994)	30		25 (83%)	5 (17%)		
Hazell et al. (1995)	127		73 (57%)	43 (34%)	11 (7%)	
Kou et al. (1994)	20	5 (25%)	7 (35%)	2 (10%)		6 (30%)
Kim et al. (1995)	13		10 (77%)	3 (23%)		
Ito (1997)	54		50 (93%)	4 (7%)		
Miyamoto et al. (1997)	48		22 (46%)	24 (50%)	2 (4%)	
Aschendorff et al. (1998)	32		22 (69%)	10 (31%)		
Demajumdar et al. (1999)	80	62 (78%)		18 (23%)		
Ruckenstein et al (2001)	39	17 (44%)	19 (49%)	3 (8%)		
Greimel et al. (2002)	26	15,40%	26,70%	50%		
Mo et al. (2002)	59	1 (2%)	32 (54%)	21 (36%)	5 (8%)	
Daneshi et al. (2005)	20	11 (55%)	5 (25%)	4 (20%)		
De Coninck et al. (2006)	91	29%	30%			
Kompis et al. (2006)	59		36 (61%)	15 (25%)	6 (10%)	2 (3%)
Yonehara et al. (2006)	21	7 (33%)	8 (38%)	6 (29%)		
Pan et al. (2009)	255	94 (37%)		150 (59%)		11 (4%)
Bovo et al. (2011)	36	13 (36%)	15 (42%)	6 (17%)	2 (6%)	
Amoodi et al. (2011)	142	53 (37%)	41 (29%)	41 (29%)	7 (5%)	
Olze et al. (2011)	39	3 (8%)	22 (56%)	14 (36%)		
Olze et a. (2012)	32	2 (6%)	26 (81%)	4 (13%)		
Kompis et al. (2012)	101	25 (25%)	60 (59%)		11 (11%)	5 (5%)
Kim et al. (2013)	35	10 (29%)	12 (34%)	13 (38%)		
Klooststra et al. (2014)	117	11 (9%)	23 (20%)	67 (57%)	5 (4%)	11 (9%)

The effect of cochlear implantation on tinnitus

The effects of implantation on tinnitus were usually assessed by standard tinnitus questionnaires. Most of the studies used validated questionnaires measuring tinnitus handicap, such as the THI (Tinnitus Handicap Inventory, the THQ (Tinnitus Handicap Questionnaire) or the TQ (Tinnitus Questionnaire) to study the effect of cochlear implantation on tinnitus. Some studies only used the opinion of the patient or a Visual Analogue Scale to assess tinnitus loudness or tinnitus burden (Table 1). Several studies have shown suppression of tinnitus loudness and burden as co-occurring effect of cochlear implantation. Suppression of tinnitus occurs in 15-95% of the cases (Akdogan, Ozcan, Ozbek, & Dere, 2009; Bovo, Ciorba, & Martini, 2011; Klooststra et al., 2015; Kompis et al., 2012; Pan et al., 2009; Quaranta et al., 2008; Rubinstein, Tyler, Johnson, & Brown, 2003; Van De Heyning et al., 2008). However, some cochlear implant patients report an exacerbation (1-10%) or the onset (0-23,5%) of tinnitus after implantation (Akdogan et al., 2009; Baguley & Atlas, 2007; Bovo et al., 2011; Klooststra et al., 2015; Kompis et al., 2012; Quaranta et al., 2008; Van De Heyning et al., 2008).

Tinnitus severity and the psychological consequences of tinnitus in cochlear implant patients

Tinnitus severity is often measured by tinnitus handicap. Tinnitus handicap describes the influence of the tinnitus on patients' life. There are a couple of studies that described the tinnitus handicap in cochlear implant candidates. As mentioned above there are three tinnitus handicap questionnaires that have been used in the studies done so far: THI (Tinnitus Handicap Inventory) (Amoodi et al., 2011; Andersson, Freijd, Baguley, & Idrizbegovic, 2009; Bovo et al., 2011; Klooststra et al., 2015), THQ (Tinnitus Handicap Questionnaire) (Klooststra et al., 2015; Pan et al., 2009) and the TQ (Tinnitus Questionnaire) (Olze, Szczepek, Haupt, Förster, et al., 2011; Olze, Szczepek, Haupt, Zirke, et al., 2011). Considering these questionnaires the mean preoperative tinnitus handicap in cochlear implant candidates is often mild to severe: THI 30.20-45.88 (total score 100), THQ 39.9-41.2 (total score 100), TQ 26.3-33.4 (total score 84). Postoperative the mean tinnitus handicap reduces to mild: THI 20.18-32.33, THQ 29.5-31.8, TQ 20.3-23.6.

The psychological and social consequences of tinnitus have not been studied extensively in the population of cochlear implant patients. According to the few studies done so far in cochlear implant (CI) patients, feelings of anxiety and

depression are not prominent in cochlear implant candidates. According to scores on the HADS (Hospital Anxiety and Depression Scale) preoperative 9-29% of the patients show severe feelings of anxiety and depression (Kloostra et al., 2015). These scores are lower compared to the general tinnitus population. In this population 21-45% of the cases show severe psychological problems (Carlsson et al., 2015). These feelings often improve after cochlear implantation (Kloostra et al., 2015; Knutson et al., 1998; Mo, Harris, & Lindbæk, 2002; Olze, Szczepek, Haupt, Förster, et al., 2011). After cochlear implantation tinnitus sometimes causes severe anxiety (14-17%) or depression (3-5%), but when there is a high tinnitus handicap postoperative this is correlated to feelings of anxiety and depression (Andersson et al., 2009; Kloostra et al., 2015; Olze, Szczepek, Haupt, Förster, et al., 2011). Also, patients who experience tinnitus onset after cochlear implantation postoperatively show more feelings of anxiety and depression than preoperatively (Kloostra et al., 2015). The improvement in feelings of anxiety and depression after cochlear implantation may result from tinnitus reduction, but more likely this is due to the improvement of the ability to hear. This is more likely because also patients who do not experience tinnitus change after cochlear implantation do show reduction in feelings of anxiety and depression after implantation (Kloostra et al., 2015). Both before and after cochlear implantation feelings of anxiety are more prominent than feelings of depression. This is consistent with the general population (12% versus 9%) and the general tinnitus population (31% versus 22%), i.e. generally feelings of anxiety are more common than feelings of depression (Carlsson et al., 2015).

Mechanisms of tinnitus change

A number of mechanisms had been proposed to explain the beneficial effect of cochlear implantation on tinnitus. Firstly the restoration of hearing in the implanted ear may cause the tinnitus to be masked by external sound. This straightforward masking effect may explain the tinnitus reduction in patients who experience the beneficial effect immediately or within a short time after the implant activation. Acoustic masking is likely involved in patients who describe tinnitus reduction only when in implant in turned on. In these patients the tinnitus reappears immediately after they switch off their device (Bovo et al., 2011; Quaranta et al., 2008).

Secondly, the sudden reactivation of afferent neurons may trigger plastic reorganisation of central auditory pathways. Since such reorganisation presumably takes months to

develop, it could play a role in patients who experience tinnitus reduction over several months after implant activation. Most probably 6 months of cochlear implant use might be enough to produce cerebral plastic reorganisation, which is able to reduce the tinnitus loudness. Also, reorganisation of the central auditory pathways could explain reduction in tinnitus loudness both with cochlear implant on and off.

Note that these mechanisms are similar to those proposed for the positive effect of hearing aid fitting on tinnitus (Hoare, Edmondson-Jones, Sereda, Akeroyd, & Hall, 2014). In both hearing aids and implants, the improved afferent input to the brain causes a reduction of the tinnitus. As discussed above, current neurophysiological models of tinnitus consider tinnitus to result from abnormal spontaneous activity in the brain due to lack of normal afferent input from the brain (Singer et al., 2013). Hence, restoration of that activity may restore normal central activity and thereby reduce tinnitus. In cochlear implant candidates, the primary reason for placing the implant is that an acoustic benefit provides insufficient hearing benefit. Apart from advantage of cochlear implantation for hearing benefit, it is unclear whether there is a specific advantage of electrical stimulation over acoustic stimulation for the suppression of tinnitus.

Also psychological factors can play a role in the positive effect of cochlear implantation on tinnitus. The major surgical procedure and positive postoperative expectations concerning tinnitus may contribute to a positive effect of cochlear implantation on tinnitus although their role is difficult to measure (Bovo et al., 2011). The cognitive dissonance theory of Festinger assumes that opposing cognitions and experiences create tension and dissonance which are undesirable (FESTINGER, 1962). Unconsciously people try to avoid these tension and dissonance. There are many studies described that show that people when they make a great investment (financial or in effort) these people afterwards experience the outcome of this investment more positive than it actually is. If you made a great effort for something that you afterwards did not like this creates cognitive dissonance. In these situations you are unconsciously inclined to evaluate this situation more positive than it actually is. We could imagine that this mechanism could also play a role after a major operation such as a cochlear implantation. It could be that patients, although the outcome was not exactly as they expected, unconsciously reduce dissonance by experiencing a positive effect on tinnitus.

Similar to hearing aid fitting, restoration of hearing by a cochlear implant may also have a negative effect on tinnitus. Some patients report a deterioration of tinnitus that already existed prior to implantation. Others report the onset of tinnitus after implant surgery

(Baguley & Atlas, 2007; Bovo et al., 2011; Quaranta et al., 2008). There are three possible methods in which cochlear implantation can cause a negative effect on tinnitus.

The deterioration or onset of tinnitus has been associated with surgical trauma. The implant surgery, particularly the electrode insertion, is potential traumatic to cochlear structures. Damage to cochlear structures may cause the loss of any residual hearing in a surgery ear. This would further reduce the afferent input to the brain, and thereby contribute to tinnitus.

The second mechanism that could cause deterioration or onset of tinnitus after cochlear implantation is based on the effect that some patients have trouble hearing the difference between external sound and their tinnitus (Quaranta et al., 2008). In these patients the percept that is associated with tinnitus may correspond to neural activity that is directly induced by stimulation of the implant. Actually, these patients do not experience tinnitus but the complaints of these patients appear to have been associated with a confusion between external sounds and tinnitus. In theory, this kind of 'tinnitus' could disappear after further revalidation, but in the current literature there are no data confirming this.

The last mechanism could again be related to psychological factors and cognitive processing. Possibly a negative effect of cochlear implantation on tinnitus could be explained by wrong coping strategies or dysfunctional cognitive processing due to unfulfilled high preoperative expectations which can both concern hearing and tinnitus. Also stress and tension around a major operation as cochlear implantation can cause tinnitus to deteriorate or to arise (Klooststra et al., 2015; Kompis et al., 2012).

Factors influencing the effect of cochlear implantation on tinnitus

Since the effect of cochlear implantation on tinnitus can be both positive and negative, there is an obvious need to predict changes in tinnitus that surround implantation. Several studies aimed to predict the effect of cochlear implantation on tinnitus (Kompis et al., 2012; Olze, Szczepek, Haupt, Förster, et al., 2011; Olze, Szczepek, Haupt, Zirke, et al., 2011; Pan et al., 2009; Souliere, Kileny, Zwolan, & Kemink, 1992).

The different studies done so far do not show consistent results. Some factors are both described as positive predictor as well as a negative predictor.

Predictors of a positive effect of cochlear implantation found in several studies were: higher preoperative tinnitus handicap scores and especially high scores in the emotional subscale of the handicap questionnaires (Olze, Szczepek, Haupt, Förster, et al., 2011; Olze, Szczepek, Haupt, Zirke, et al., 2011; Pan et al., 2009; Souliere et al., 1992), higher age at implantation, higher preoperative hearing handicap scores (Amoodi et al., 2011), higher preoperative stress levels (Olze, Szczepek, Haupt, Förster, et al., 2011; Olze, Szczepek, Haupt, Zirke, et al., 2011), and less years of hearing loss (Olze, Szczepek, Haupt, Förster, et al., 2011; Olze, Szczepek, Haupt, Zirke, et al., 2011). However, another study described that there was no relationship between a positive effect of implantation on tinnitus and age at implantation, years of tinnitus before implantation and the level of hearing loss before implantation (Kompis et al., 2012).

Considering the possible factors predicting a negative effect of cochlear implantation on tinnitus, i.e. tinnitus deterioration or tinnitus onset, a higher age at implantation, higher preoperative tinnitus handicap scores (Pan et al., 2009), better hearing before implantation, shorter period of hearing loss before implantation, higher additional hearing loss after implantation and worse phoneme scores after implantation are described to be correlated to a negative effect of implantation on tinnitus (Kompis et al., 2012). However, most of these correlations lack of significance (Kompis et al., 2012).

The relationship between the amount of preoperative hearing loss, preoperative hearing handicap and the effect of cochlear implantation on tinnitus seems to be the only consistent predictor. While worse hearing and a higher hearing handicap before implantation are predictors of a positive effect of cochlear implantation on tinnitus, are better preoperative hearing and less preoperative hearing handicap predictors of a negative effect of cochlear implantation on tinnitus. However, also considering this factor there is a study that described no relation between the level of hearing loss and the effect of cochlear implantation on tinnitus (Kompis et al., 2012). The fact that several studies described preoperative hearing and preoperative handicap as predictors of cochlear implantation on tinnitus is rather straightforward. The worse the preoperative hearing is, the more postoperative improvement is possible both concerning hearing and tinnitus. On the other hand the better preoperative hearing, the more postoperative deterioration is possible concerning hearing and tinnitus.

There are also some postoperative factors considering hearing that correlate with a negative effect of cochlear implantation on tinnitus, namely higher postoperative additional hearing loss and low postoperative phoneme scores. Both these factors can

be caused by additional preoperative cochlear injury due to electrode insertion. Besides, low postoperative phoneme scores can also cause disappointment in patients. Possibly these patients with low postoperative phoneme scores have unfulfilled high preoperative expectations considering their hearing. These unfulfilled expectations can cause a negative feeling about the implantation and can in this way also have negative influence on postoperative outcome considering tinnitus (Bovo et al., 2011).

Higher preoperative tinnitus handicap is described as predictor of both a positive and a negative effect of cochlear implantation on tinnitus. Considering a higher preoperative tinnitus handicap as a predictor of a positive effect on tinnitus this could again be explained by the fact that this causes a worse preoperative situation and more space for postoperative improvement concerning tinnitus. Concerning higher preoperative tinnitus handicap scores as a predictor of a negative effect there is also a possible explanation. Previous studies described a relationship between higher tinnitus handicap scores and personality D characteristics in the general tinnitus population (Bartels et al., 2010). This relationship has not been investigated yet in the specific population of cochlear implant recipients. Personality D is characterised by social inhibition and negative affectivity. Therefore, type D patients tend to experience more negative emotions, generally feel sad and have a gloomy view of life, while not sharing these emotions with others due to fears of how they may react (Bartels et al., 2010). Possibly, patients with type D personality are more prone to a negative effect of cochlear implantation on tinnitus and this may explain why patients with higher preoperative tinnitus handicap scores experience more often a negative effect of cochlear implantation on tinnitus.

Less years of hearing loss and tinnitus are also described as predictors of both a positive and negative effect of cochlear implantation on tinnitus. However, concerning these predictors there is another study that described no effect between the years of hearing loss and tinnitus before implantation and a positive effect of cochlear implantation on tinnitus. The less years of hearing loss as a predictor of a positive effect of cochlear implantation on tinnitus can be associated with the theory that in hearing loss and tinnitus there occurs a reorganisation in the central auditory pathways. Maybe the shorter the hearing loss and tinnitus exists the less reorganisation has taken place and the easier this process is reversed. The reason why a shorter time of hearing also can be a predictor of a negative effect on tinnitus is hard to explain.

The higher age at implantation as a predictor of both a positive effect and negative effect of cochlear implantation on tinnitus is also difficult to explain. Besides, the fact that

another study described no relationship between age at implantation and the effect of cochlear implantation on tinnitus makes this predictor questionable.

Maybe the contradiction and the lack of significance in the results considering predictors of the effect of cochlear implantation on tinnitus can be explained by the couple of problems that can occur in the research concerning the effect of cochlear implantation on tinnitus and the factors influencing this effect.

First most studies done so far had a retrospective design. A retrospective design has one major disadvantage, namely that it is prone to recall bias. Because the time between the implantation and the administering of the questionnaires can be long, this can cause the patients not to remember the situation before the implantation very well at the time the questionnaires are filled in. This could magnify effects. This means that patients who experienced a positive effect of cochlear implantation on tinnitus remember the situation before implantation worse than it actually was and the same applies for patients who experienced a negative effect of cochlear implantation on tinnitus; they can remember the preoperative situation more positive than it actually was.

However, there is also one major benefit of a retrospective study design; effects caused by response shift are expected to be small. Response shift means that people tend to change their internal standards and values after they experience a relevant change in health (Schwartz et al., 2006). After a positive change in their health situation, for example cochlear implantation, people tend to be more demanding concerning their current quality of life. In a study design in which patients are asked to fill in questionnaires both before and after implantation, i.e. a pretest/posttest design, this can cause an underestimation of the change between pre- and posttest values. With a retrospective design, in which both measures are administered at the same time, this bias is not likely to occur.

The last problem in the research concerning the effect of cochlear implantation on tinnitus and the factors influencing the effect of cochlear implantation on tinnitus is social desirability and effort justification. This could cause patients to fulfil the expectations of the researchers and can be in favour of a positive effect of cochlear implantation on tinnitus.

Stimulation strategies

The exact mechanism explaining how electrical stimulation by a cochlear implant reduces tinnitus is still unclear. As mentioned earlier masking seems to play an important part, but also some (central) nervous system effect seems to play a part in the influence of electric stimulation on tinnitus suppression (Aran & Cazals, 2008; Battmer, Heermann, & Laszig, 1989; Cazals, Negrevergne, & Aran, 1978; Di Nardo et al., 2009; Hazell, Meerton, & Conway, 1989; Konopka, Zalewski, Olszewski, Olszewska-Ziaber, & Pietkiewicz, 2001; Okusa, Shiraishi, Kubo, & Matsunaga, 1993; Portmann, Cazals, Negrevergne, & Aran, 1979; Rubinstein et al., 2003; Watanabe, Okawara, Baba, & Yagi, 1997). Cochlear implants use alternating current rather than direct current stimulation (Daneshi, Mahmoudian, Farhadi, Hasanzadeh, & Ghaleboghi, 2005). Some studies suggested that particular electrical stimulation strategies may be beneficial for suppression of tinnitus by a cochlear implant. Chang et al described that stimulation with loud sounds is more effective than stimulation with soft sounds in the suppression of tinnitus (Chang & Zeng, 2012). However, Rubinstein et al found that some patients experience improvement of tinnitus without the stimulus being louder than the tinnitus (Rubinstein et al., 2003). Considering the place of stimulation Zeng et al found that stimulation at an apical electrode is more effective in reducing tinnitus than stimulation in a distal electrode (Zeng et al., 2011). In previous studies there are multiple theories about pulse rates and the degree of tinnitus reduction. High-rate stimulation seems to restore spontaneous activity at the peripheral level, but is not effective in inducing central activity. In contrast, low-rate stimulation seems to induce activity at thalamocortical level (Rubinstein et al., 2003; Zeng et al., 2011).

Imaging of tinnitus in cochlear implant patients

The fact that some cochlear implant recipients have control over the loudness of their tinnitus offers a unique opportunity for neuroimaging studies. In this way the relationship between brainactivity and tinnitus can be studied well. However, a drawback is that a cochlear implant is not compatible with most neuroimaging machines and techniques. For example current cochlear implants are not usable in an MRI scanner, because of the magnet that is included in the cochlear implant. That is why not many studies have been done so far studying the effect of central nervous activation in tinnitus patients with a cochlear implant. Another imaging modality to study neural activity in the human brain is PET (Positron Emission Tomography) scanning. This imaging modality is usable in

cochlear implant recipients. Labelled water PET scans are, with a half-life time of two minutes, the PET scans with the best temporal resolution and are the best type of PET scans for detecting changes in neural cortical activity. The two studies done so far in cochlear implant patients used labelled water PET scans to image the central nervous system activity.

Mirz et al found that use of cochlear implants reduced signs of tinnitus-related activity in primary auditory and associate cortices (Mortensen, Mirz, & Gjedde, 2006). Besides activity in the auditory cortices Mirz et al also found tinnitus related activity in the areas of the central nervous system associated with emotion (limbic system) and attention (dorsolateral prefrontal cortices) (Mortensen et al., 2006).

The study of Osaki et al on three male cochlear implant patients identified that there is activation of the anterior part of the temporal cortex during a period of residual inhibition of tinnitus after turning the cochlear implant off (Osaki et al., 2005). This study also described activation of the cerebellum during the perception of tinnitus (Osaki et al., 2005).

The primary auditory cortex (PAC) is important in sound perception and it seems likely to assume that (asymmetric) neural activity in the PAC plays some role in all human sound perception, including tinnitus. Involvement of the PAC in tinnitus is confirmed by the greater part of the previous done neuro-imaging studies (Arnold, Bartenstein, Oestreicher, Römer, & Schwaiger, 1996; Eichhammer, Hajak, Kleinjung, Landgrebe, & Langguth, 2007; Langguth et al., 2006; Lanting, de Kleine, & van Dijk, 2009; Lobarinas, Sun, Stolzberg, Lu, & Salvi, 2008; Lockwood et al., 1998; Mirz et al., 1999). Many studies, both animal and human studies, show that the secondary auditory cortex and the auditory association cortex behave differently in patients with tinnitus, while this behaviour in the PAC is not always clearly observed. This bypass suggests involvement of the non-classical auditory pathway in tinnitus perception, which directly projects from the medial geniculate body to the auditory association cortex (Eichhammer et al., 2007; Lanting et al., 2009; Lobarinas et al., 2008; Mirz, Gjedde, Ishizu, & Pedersen, 2000; Mirz et al., 1999).

Severe tinnitus represents a failure of habituation and potentiates an annoying effect by enhancement of negative beliefs. These failure of habituation and annoying effect are thought to be caused by the threat to personal integrity (fear of having tinnitus the rest of the life, fear of a potentially lethal disease causing the tinnitus, etc.) what leads to maintenance of the activation of brain regions normally engaged in interaction with the

exterior environment, such as the limbic system and the frontal cortex (Eichhammer et al., 2007; Langguth et al., 2006; Lanting et al., 2009; Lobarinas et al., 2008; Lockwood et al., 1998; Mirz et al., 2000, 1999; Plewnia et al., 2007).

The cerebellum seem to have an increased activity during the presentation of aversive sounds, but the association of the cerebellum with tinnitus is not substantially supported by previous done neuro-imaging studies in the general tinnitus population (Lanting et al., 2009; Shulman, Strashun, Avitable, Lenhardt, & Goldstein, 2004).

Cochlear implantation in patients with single sided deafness and tinnitus

The effect of cochlear implantation on tinnitus is mostly positive. Therefore, suppression of tinnitus has also been proposed as a possible primary objective of cochlear implantation. For example, several research projects explored the effect on tinnitus in patient with single sided deafness. Single-sided deaf patients would normally not be considered for cochlear implantation, since the single normal hearing ear is generally considered sufficient for most auditory communication. However, subjects with single sided deafness may experience debilitating tinnitus in de deaf ear, for which an effective treatment would be very welcome.

In the 14 studies done so far most studies included patients with single sided deafness and unilateral incapacitating tinnitus on the side of the hearing loss, although a couple of studies also included patients with bilateral or central invalidating tinnitus. Most of the included patients showed improvement of tinnitus or complete suppression after cochlear implantation. These positive results include both tinnitus distress and tinnitus loudness. A minority of the patients reported that their tinnitus did not change after the implantation and none of the patients reported tinnitus worsening after the operation (table 2). Besides, most studies reported that the positive effect of a cochlear implant on tinnitus only existed with the cochlear implant turned on. After turning off the cochlear implant the tinnitus reoccured within seconds to hours. Only one study reported that improvement in tinnitus perception remained after cochlear implant deactivation (Ramos et al., 2012). Also, one study reported that the tinnitus worsened after cochlear implant deactivation compared to the initial tinnitus loudness (Arndt et al., 2010). The fact that tinnitus in most patients reoccurs after switching off de device supports the theory that tinnitus results from cochlear deafferentiation (Van De Heyning et al., 2008).

Table 2: effect of cochlear implantation on tinnitus in patients with single sided deafness

Study	Number of patients	Outcome measures	Effect on tinnitus		
			Tinnitus disappeared	Tinnitus improved	Unchanged tinnitus
Van de Heyning et al. (2008)	22	TQ, VAS-loudness	3	18	1
Kleinjung et al. (2009)	1	THI, TQ, VAS-loudness	1		
Palau et al. (2010)	3	THI, VAS-loudness	1	2	
Buechner et al. (2010)	5	VAS-loudness		5	
Arndt et al. (2010)	10	VAS-loudness	5	3	2
Jacob et al. (2011)	11	No quantification		9	2
Ramos et al. (2012)	10	THI, VAS-loudness	2	7	1
Kleine Punte et al. (2011)	26	VAS-loudness	4	22	
Zengt et al. (2011)	1	VAS-loudness	1		
Song et al. (2013)	9	TQ, VAS-loudness		9	
Kleine Punte et al. (2013)	7	TQ, VAS-loudness		7	
Tavora-Vieira et al. (2013)	9	TRQ		7	
Gartrell et al. (2014)	1	TRQ, THI, TQ		1	

However, the improved hearing after cochlear implantation can also serve as tinnitus masker.

The results of cochlear implantation for tinnitus in single-sided deafness so far are promising. However, the results have to be considered with caution because only one study used a control group and all studies lack blinding and included a limited number of participants.

REFERENCES

- Akdogan, O., Ozcan, I., Ozbek, C., & Dere, H. (2009). Tinnitus after cochlear implantation. *Auris Nasus Larynx*. <https://doi.org/10.1016/j.anl.2008.04.005>
- Amoodi, H. A., Mick, P. T., Shipp, D. B., Friesen, L. M., Nedzelski, J. M., Chen, J. M., & Lin, V. Y. W. (2011). The effects of unilateral cochlear implantation on the tinnitus handicap inventory and the influence on quality of life. *Laryngoscope*. <https://doi.org/10.1002/lary.21851>
- Andersson, G., Freijd, A., Baguley, D. M., & Idrizbegovic, E. (2009). Tinnitus Distress, Anxiety, Depression, and Hearing Problems among Cochlear Implant Patients with Tinnitus. *Journal of the American Academy of Audiology*. <https://doi.org/10.3766/jaaa.20.5.5>
- Aran, J. M., & Cazals, Y. (2008). Electrical Suppression of Tinnitus. In *Tinnitus*. <https://doi.org/10.1002/9780470720974.ch13>
- Arndt, S., Beck, R., Schild, C., Grauvogel, T. D., Laszig, R., & Aschendorff, A. (2010). Management of cochlear implantation in patients with malformations. *Clinical Otolaryngology*. <https://doi.org/10.1111/j.1749-4486.2010.02124.x>
- Arnold, W., Bartenstein, P., Oestreicher, E., Römer, W., & Schwaiger, M. (1996). Focal metabolic activation in the predominant left auditory cortex in patients suffering from tinnitus: A PET study with [¹⁸F]Deoxyglucose. *ORL*. <https://doi.org/10.1159/000276835>
- Baguley, D. M., & Atlas, M. D. (2007). Cochlear implants and tinnitus. *Progress in Brain Research*. [https://doi.org/10.1016/S0079-6123\(07\)66033-6](https://doi.org/10.1016/S0079-6123(07)66033-6)
- Bartels, H., Pedersen, S. S., Van Der Laan, B. F. A. M., Staal, M. J., Albers, F. W. J., & Middel, B. (2010). The impact of type D personality on health-related quality of life in tinnitus patients is mainly mediated by anxiety and depression. *Otology and Neurotology*. <https://doi.org/10.1097/MAO.0b013e3181bc3dd1>
- Battmer, R. D., Heermann, R., & Laszig, R. (1989). [Suppression of tinnitus by electric stimulation in cochlear implant patients]. *HNO*.
- Berliner, K. I., Shelton, C., Hitselberger, W. E., & Luxford, W. M. (1992). Acoustic tumors: Effect of surgical removal on tinnitus. *Otology and Neurotology*. <https://doi.org/10.1097/00129492-199201000-00005>
- Bovo, R., Ciorba, A., & Martini, A. (2011). Tinnitus and cochlear implants. *Auris Nasus Larynx*. <https://doi.org/10.1016/j.anl.2010.05.003>
- Schwartz, C.E., Bode, R., Repucci, N., Becker, J., Sprangers, M.A.G., Fayers, P.M. (2006). The clinical significance of adaptation to changing health: A meta-analysis of response shift. *Quality of Life Research*.
- Carlsson, P. I., Hjalldahl, J., Magnuson, A., Ternevall, E., Edén, M., Skagerstrand, A., & Jönsson, R. (2015). Severe to profound hearing impairment: Quality of life, psychosocial consequences and audiological rehabilitation. *Disability and Rehabilitation*. <https://doi.org/10.3109/09638288.2014.982833>

- Cazals, Y., Negrevergne, M., & Aran, J. M. (1978). Electrical stimulation of the cochlea in man: hearing induction and tinnitus suppression. *Journal of the American Auditory Society*.
- Chang, J. E., & Zeng, F. G. (2012). Tinnitus suppression by electric stimulation of the auditory nerve. *Frontiers in Systems Neuroscience*. <https://doi.org/10.3389/fnsys.2012.00019>
- Coles, R. R. A. (1984). Epidemiology of tinnitus: (1) Prevalence. *The Journal of Laryngology, Rhinology, and Otology*. <https://doi.org/10.1017/S1755146300090041>
- Daneshi, A., Mahmoudian, S., Farhadi, M., Hasanzadeh, S., & Ghalebagh, B. (2005). Auditory electrical tinnitus suppression in patients with and without implants. *International Tinnitus Journal*.
- Di Nardo, W., Cianfrone, F., Scorpecci, A., Cantore, I., Giannantonio, S., & Paludetti, G. (2009). Transtympanic electrical stimulation for immediate and long-term tinnitus suppression. In *International Tinnitus Journal*.
- Eggermont, J. J., & Komiya, H. (2000). Moderate noise trauma in juvenile cats results in profound cortical topographic map changes in adulthood. *Hearing Research*. [https://doi.org/10.1016/S0378-5955\(00\)00024-1](https://doi.org/10.1016/S0378-5955(00)00024-1)
- Eggermont, J. J., & Roberts, L. E. (2004). The neuroscience of tinnitus. *Trends in Neurosciences*. <https://doi.org/10.1016/j.tins.2004.08.010>
- Eichhammer, P., Hajak, G., Kleinjung, T., Landgrebe, M., & Langguth, B. (2007). Functional imaging of chronic tinnitus: the use of positron emission tomography. *Progress in Brain Research*. [https://doi.org/10.1016/S0079-6123\(07\)66008-7](https://doi.org/10.1016/S0079-6123(07)66008-7)
- FESTINGER, L. (1962). Cognitive dissonance. *Scientific American*. <https://doi.org/10.1038/scientificamerican1062-93>
- Hazell, J. W. P., Meerton, L. J., & Conway, M. J. (1989). Electrical tinnitus suppression (ETS) with a single channel cochlear implant. *Journal of Laryngology and Otology*.
- Hoare, D. J., Edmondson-Jones, M., Sereda, M., Akeroyd, M. A., & Hall, D. (2014). Amplification with hearing aids for patients with tinnitus and co-existing hearing loss. *Cochrane Database of Systematic Reviews*. <https://doi.org/10.1002/14651858.CD010151.pub2>
- House, W. F., Berliner, K., & Crary, W. (1976). Cochlear implants. *Annals of Otology, Rhinology and Laryngology*. <https://doi.org/10.1177/00034894760850s303>
- Kaltenbach, J. A. (2000). Neurophysiologic mechanisms of tinnitus. *Journal of the American Academy of Audiology*.
- Kiang, N. Y., Moxon, E. C., & Levine, R. A. (1970). Auditory-nerve activity in cats with normal and abnormal cochleas. In: *Sensorineural hearing loss. Ciba Foundation Symposium*.
- Kim, D. K., Bae, S. C., Park, K. H., Jun, B. C., Lee, D. H., Yeo, S. W., & Park, S. N. (2013). Tinnitus in patients with profound hearing loss and the effect of cochlear implantation. *European Archives of Oto-Rhino-Laryngology*. <https://doi.org/10.1007/s00405-012-2193-2>
- Kloostra, F. J. J., Arnold, R., Hofman, R., & Van Dijk, P. (2015). Changes in tinnitus after cochlear

- implantation and its relation with psychological functioning. *Audiology and Neurotology*. <https://doi.org/10.1159/000365959>
- Knutson, J. F., Murray, K. T., Husarek, S., Westerhouse, K., Woodworth, G., Gantz, B. J., & Tyler, R. S. (1998). Psychological change over 54 months of cochlear implant use. *Ear and Hearing*. <https://doi.org/10.1097/00003446-199806000-00003>
- Kompis, M., Pelizzone, M., Dillier, N., Allum, J., Demin, N., & Senn, P. (2012). Tinnitus before and 6 months after cochlear implantation. *Audiology and Neurotology*. <https://doi.org/10.1159/000335126>
- Konopka, W., Zalewski, P., Olszewski, J., Olszewska-Ziaber, A., & Pietkiewicz, P. (2001). Tinnitus suppression by electrical promontory stimulation (EPS) in patients with sensorineural hearing loss. *Auris Nasus Larynx*. [https://doi.org/10.1016/S0385-8146\(00\)00086-9](https://doi.org/10.1016/S0385-8146(00)00086-9)
- Langguth, B., Eichhammer, P., Kreutzer, A., Maenner, P., Marienhagen, J., Kleinjung, T., ... Hajak, G. (2006). The impact of auditory cortex activity on characterizing and treating patients with chronic tinnitus - First results from a PET study. In *Acta Oto-Laryngologica*. <https://doi.org/10.1080/03655230600895317>
- Lanting, C. P., de Kleine, E., & van Dijk, P. (2009). Neural activity underlying tinnitus generation: Results from PET and fMRI. *Hearing Research*. <https://doi.org/10.1016/j.heares.2009.06.009>
- Lobarinas, E., Sun, W., Stolzberg, D., Lu, J., & Salvi, R. (2008). Human brain imaging of tinnitus and animal models. *Seminars in Hearing*. <https://doi.org/10.1055/s-0028-1095893>
- Lockwood, A. H., Salvi, R. J., Coad, M. L., Towsley, M. L., Wack, D. S., & Murphy, B. W. (1998). The functional neuroanatomy of tinnitus: Evidence for limbic system links and neural plasticity. *Neurology*. <https://doi.org/10.1212/WNL.50.1.114>
- Mirz, F., Gjedde, A., Ishizu, K., & Pedersen, C. B. (2000). Cortical networks subserving the perception of tinnitus - A PET study. In *Acta Oto-Laryngologica, Supplement*. <https://doi.org/10.1080/000164800454503>
- Mirz, F., Pedersen, C. B., Ishizu, K., Johannsen, P., Ovesen, T., Stødkilde-Jørgensen, H., & Gjedde, A. (1999). Positron emission tomography of cortical centers of tinnitus. *Hearing Research*. [https://doi.org/10.1016/S0378-5955\(99\)00075-1](https://doi.org/10.1016/S0378-5955(99)00075-1)
- Mo, B., Harris, S., & Lindbæk, M. (2002). Tinnitus in cochlear implant patients - A comparison with other hearing-impaired patients. *International Journal of Audiology*. <https://doi.org/10.3109/14992020209056073>
- Møller, A. R. (2003). Pathophysiology of tinnitus. *Otolaryngologic Clinics of North America*. [https://doi.org/10.1016/S0030-6665\(02\)00170-6](https://doi.org/10.1016/S0030-6665(02)00170-6)
- Mortensen, M. V., Mirz, F., & Gjedde, A. (2006). Restored speech comprehension linked to activity in left inferior prefrontal and right temporal cortices in postlingual deafness. *NeuroImage*. <https://doi.org/10.1016/j.neuroimage.2005.12.020>
- Okusa, M., Shiraishi, T., Kubo, T., & Matsunaga, T. (1993). Tinnitus suppression by electrical

- promontory stimulation in sensorineural deaf patients. *Acta Oto-Laryngologica*. <https://doi.org/10.3109/00016489309126215>
- Olze, H., Szczepek, A. J., Haupt, H., Förster, U., Zirke, N., Gräbel, S., & Mazurek, B. (2011). Cochlear implantation has a positive influence on quality of life, tinnitus, and psychological comorbidity. *Laryngoscope*. <https://doi.org/10.1002/lary.22145>
- Olze, H., Szczepek, A. J., Haupt, H., Zirke, N., Graebel, S., & Mazurek, B. (2011). The impact of cochlear implantation on tinnitus, stress and quality of life in postlingually deafened patients. *Audiology and Neurotology*. <https://doi.org/10.1159/000323847>
- Pan, T., Tyler, R. S., Ji, H., Coelho, C., Gehringer, A. K., & Gogel, S. A. (2009). Changes in the tinnitus handicap questionnaire after cochlear implantation. *American Journal of Audiology*. [https://doi.org/10.1044/1059-0889\(2009/07-0042\)](https://doi.org/10.1044/1059-0889(2009/07-0042))
- Plewnia, C., Reimold, M., Najib, A., Reischl, G., Plontke, S. K., & Gerloff, C. (2007). Moderate therapeutic efficacy of positron emission tomography-navigated repetitive transcranial magnetic stimulation for chronic tinnitus: A randomised, controlled pilot study. *Journal of Neurology, Neurosurgery and Psychiatry*. <https://doi.org/10.1136/jnnp.2006.095612>
- Portmann, M., Cazals, Y., Negrevergne, M., & Aran, J. M. (1979). Temporary tinnitus suppression in man through electrical stimulation of the cochlea. *Acta Oto-Laryngologica*. <https://doi.org/10.3109/00016487909126423>
- Preece, J. P., Tyler, R. S., & Noble, W. (2003). The management of tinnitus. *Geriatrics and Aging*.
- Quaranta, N., Fernandez-Vega, S., D'Elia, C., Filipo, R., & Quaranta, A. (2008). The effect of unilateral multichannel cochlear implant on bilaterally perceived tinnitus. *Acta Oto-Laryngologica*. <https://doi.org/10.1080/00016480701387173>
- Ramos, Á., Polo, R., Masgoret, E., Artiles, O., Lisner, I., Zaballos, M. L., ... Osorio, Á. (2012). Cochlear implant in patients with sudden unilateral sensorineural hearing loss and associated tinnitus | Implante coclear en pacientes con hipoacusia súbita unilateral y acúfeno asociado. *Acta Otorrinolaringologica Espanola*. <https://doi.org/10.1016/j.otorri.2011.07.004>
- Roberts, L. E., Eggermont, J. J., Caspary, D. M., Shore, S. E., Melcher, J. R., & Kaltenbach, J. A. (2010). Ringing ears: The neuroscience of tinnitus. In *Journal of Neuroscience*. <https://doi.org/10.1523/JNEUROSCI.4028-10.2010>
- Rubinstein, J. T., Tyler, R. S., Johnson, A., & Brown, C. J. (2003). Electrical suppression of tinnitus with high-rate pulse trains. *Otology and Neurotology*. <https://doi.org/10.1097/00129492-200305000-00021>
- Shargorodsky, J., Curhan, G. C., & Farwell, W. R. (2010). Prevalence and characteristics of tinnitus among US adults. *American Journal of Medicine*. <https://doi.org/10.1016/j.amjmed.2010.02.015>
- Shulman, A., Strashun, A. M., Avitable, M. J., Lenhardt, M. L., & Goldstein, B. A. (2004). Ultra-high-frequency acoustic stimulation and tinnitus control: A positron emission tomography study. *International Tinnitus Journal*.

- Silverstein, H. (1976). Transmeatal labyrinthectomy with and without cochleovestibular neurectomy. *The Laryngoscope*. <https://doi.org/10.1002/lary.5540861201>
- Singer, W., Zuccotti, A., Jaumann, M., Lee, S. C., Panford-Walsh, R., Xiong, H., ... Knipper, M. (2013). Noise-induced inner hair cell ribbon loss disturbs central arc mobilization: A novel molecular paradigm for understanding tinnitus. *Molecular Neurobiology*. <https://doi.org/10.1007/s12035-012-8372-8>
- Souliere, C. R., Kileny, P. R., Zwolan, T. A., & Kemink, J. L. (1992). Tinnitus Suppression Following Cochlear Implantation: A Multifactorial Investigation. *Archives of Otolaryngology--Head and Neck Surgery*. <https://doi.org/10.1001/archotol.1992.01880120017004>
- Tyler, R. S. (1984). Does Tinnitus Originate From Hyperactive Nerve Fibers In The Cochlea? *The Journal of Laryngology, Rhinology, and Otolaryngology*. <https://doi.org/10.1017/S1755146300090090>
- Van De Heyning, P., Vermeire, K., Diebl, M., Nopp, P., Anderson, I., & De Ridder, D. (2008). Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation. *Annals of Otolaryngology, Rhinology and Laryngology*. <https://doi.org/10.1177/000348940811700903>
- Wang, J., Salvi, R. J., & Powers, N. (1996). Plasticity of response properties of inferior colliculus neurons following acute cochlear damage. *Journal of Neurophysiology*. <https://doi.org/10.1152/jn.1996.75.1.171>
- Watanabe, K., Okawara, D., Baba, S., & Yagi, T. (1997). Electrocochleographic analysis of the suppression of tinnitus by electrical p... *Audiology*.
- Osaki, Y., Nishimura, H., Takasawa, M., Imaizuma, M., Kawashima, T., Iwaki, T., Oku, N., Hashikawa, K., Doi, K., Nishimura, T., Hatazawa, J., Kubo, T. (2005). Neural mechanism of residual inhibition of tinnitus in cochlear implant users. *NeuroReport*. <https://doi.org/10.1097/01.wnr.0000183899.85277.08> LK - <http://sfx.library.uu.nl/utrecht?sid=EMBASE&issn=09594965&id=doi:10.1097%2F01.wnr.0000183899.85277.08>
- Zeng, F. G., Tang, Q., Dimitrijevic, A., Starr, A., Larky, J., & Blevins, N. H. (2011). Tinnitus suppression by low-rate electric stimulation and its electrophysiological mechanisms. *Hearing Research*. <https://doi.org/10.1016/j.heares.2011.03.010>

3

CHANGES IN TINNITUS AFTER COCHLEAR IMPLANTATION AND ITS RELATION WITH PSYCHOLOGICAL FUNCTIONING

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ABSTRACT

This study retrospectively assessed the prevalence of tinnitus in cochlear implant patients and the changes after implantation in 212 patients implanted between 2000 and 2009. Patients were included at least 6 months after implantation and received 2 sets of questionnaires; one about the situation before implantation and one about the situation after implantation. Mostly standardized questionnaires assessed tinnitus handicap (THI, THQ), tinnitus characteristics, hearing loss (APHAB) and anxiety/depression (HADS). Of the approached patients 117 completed the full sets of questionnaires and 35 patients completed a short version. Preoperative tinnitus was reported by 51.3% of these patients, of which 55.6% reported a reduction or cessation of their tinnitus after implantation. However, 8.2 % of the patients with tinnitus reported a postoperative deterioration of their tinnitus. In addition, among the patients without preoperative tinnitus 19.6% reported the start of tinnitus after implantation. The self-reported change of tinnitus correlated with the pre- and postoperative scores on the THI and THQ. The THQ showed slightly more changes in scores after cochlear implantation compared to the THI. Overall hearing handicap and feelings of anxiety and depression decreased after implantation. In conclusion, tinnitus is reduced after cochlear implantation in an important part of the patients, but in a small part implantation has a negative effect on tinnitus. When tinnitus starts after implantation, the tinnitus handicap is mild.

INTRODUCTION

Tinnitus is a common phenomenon among cochlear implant candidates and cochlear implant users. Previous studies have described a prevalence of tinnitus in cochlear implant candidates ranging from 63-100%, with a mean prevalence of 80% [Kompis et al., 2012, Kim et al., 2012, Quaranta et al., 2008, Baguley and Atlas 2007].

The presence of tinnitus in this population is consistent with a prevailing hypothesis on the origin of tinnitus: that it arises as a response of the central auditory system to peripheral hearing loss [Roberts et al., 2010, Berliner et al., 1992, Silverstein 1976, Tyler 1983]. Peripheral hearing loss results in a decrease of afferent input to the brainstem. This may result in a change of spontaneous neural activity, which is believed to potentially cause tinnitus [Eggermont and Komiya 2000, Eggermont and Roberts 2004, Kaltenbach 2000, Kiang et al., 1970, Moller 1984, Wang et al., 1996, Preece et al., 2003].

The consequences of tinnitus vary a lot across individuals: it can be mild and cause no problems in daily life. However, tinnitus can also severely affect the psychological status and social functioning. Then, an individual may decide to seek medical help. Several psychological and social problems have been associated with tinnitus. Feelings of stress, fatigue or insomnia exist in 25-93% of the patients. Interference with work occurs in 42% of the patients, because patients with tinnitus may suffer from concentration problems. Also tinnitus is associated with agitation, which causes negative effects of tinnitus on personal relationships in 41%. In 21-63% of the tinnitus patients, the condition is associated with with more severe psychosocial problems like depression or mood disorders. Anxiety disorders exist in about 45% of the patients and some of these patients even experience suicidal feelings [Holmes and Padgham 2009, Tyler and Baker 1983, Stouffer and Tyler 1990, Andersson et al., 2002, Lockwood et al., 2002, Zoger et al., 2001].

The psychological and social consequences of tinnitus have been studied less extensively in populations with cochlear implant patients. Until now, only a couple of studies investigated the effect of tinnitus on feelings of anxiety and depression in this population. According to these studies in cochlear implant (CI) patients, feelings of anxiety and depression often improve after cochlear implantation [Mo et al., 2005, Knutson et al., 1998, Olze et al., 2011]. After cochlear implantation tinnitus seldomly causes anxiety (14%) and depression (5%), but when there is a high tinnitus handicap postoperative this is correlated with feelings of anxiety and depression [Olze et al., 2011, Andersson et al., 2009].

Many studies have shown suppression of tinnitus as co-occurring effect of cochlear implantation. The first report of subjective tinnitus being suppressed by a cochlear implant was published by House in 1976 [House 1976]. After that, several studies have confirmed these results, showing that suppression of tinnitus occurs in 15-95% of the cases [Kompis et al., 2012, Quaranta et al., 2008, Van de Heyning et al., 2008, Akdogan et al., 2009, Bovo et al., 2010, Pan et al., 2009, Rubinstein et al., 2003]. However, some cochlear implant patients have reported an exacerbation (1-10%) or the onset (0-23,5%) of tinnitus after implantation [Kompis et al., 2012, Quaranta et al., 2008, Baguley and Atlas 2007, Akdogan et al., 2009, Bovo et al., 2010]. Other remarkable effects of unilateral cochlear implantation are the reduction of tinnitus in the contralateral ear and the existence of residual inhibition of tinnitus after switching off the cochlear implant [Quaranta et al., 2008, Baguley and Atlas 2007].

In summary, the potential positive effect of cochlear implantation on tinnitus has been well documented. However, cochlear implantation may also have a negative effect on tinnitus. This is a concern since cochlear implantation is now being used as a treatment for tinnitus [Van de Heyning et al., 2008, Arts et al., 2012]. It is still unclear what the psychological and social consequences are in relation to the potential positive and negative effect of cochlear implantation on tinnitus, respectively. Therefore our study aims to address the prevalence of tinnitus in cochlear implant patients and the changes after cochlear implantation with respect to tinnitus, tinnitus handicap and anxiety or depression. Compared to other studies our study is unique in the fact that we used two types of tinnitus handicap questionnaires in one study and in this way could make a comparison between the scores of these two questionnaires.

MATERIALS AND METHODS

Procedure and Inclusion

Patients were recruited from the patient database of Cochlear Implant North Netherlands (CINN), the team for cochlear implantation of the University Medical Center Groningen (UMCG), The Netherlands. All patients older than 18 years of age at time of implantation, who had received their implants between 2000 and 2009 and had used their cochlear implant for at least six months, were approached for inclusion.

The study was approved by the Medical Ethics Committee of the University Medical Center Groningen. Before participation all patients gave their written informed consent.

Measures

Information about audiological tests, date of implantation, diagnosis, surgery, complications and processor type was gathered from the patients' clinical files. Besides this information we retrospectively sent the patients two questionnaire booklets. The questionnaire booklets were sent at one time, this means that we used a so called 'thentest' design. One booklet assessed the situation before the implantation and the second booklet assessed the situation after the implantation. Each booklet contained a number of questionnaires on hearing, tinnitus handicap, tinnitus characteristics and anxiety or depression. All patients completed questionnaires about hearing status, anxiety and depression. The questionnaires about tinnitus were completed only, when the patient (had) experienced tinnitus before or after implantation. We instructed the patient to fill out first the booklet assessing the situation before cochlear implantation and to fill out second the booklet assessing the situation after cochlear implantation.

The questionnaire booklet assessing the situation after implantation started with the following question: *'Were there any changes concerning your tinnitus after cochlear implantation?'*; A) No, I did not experience tinnitus before neither after implantation B) No, my already existing tinnitus remained the same after implantation C) Yes, I started to experience tinnitus after implantation D) Yes, my already existing tinnitus got worse after implantation E) Yes, my already existing tinnitus got better after implantation F) Yes, the tinnitus I experienced before implantation disappeared after implantation. This question allowed us for a comparison of various patient characteristics in relation to the observed changes in tinnitus. The outcome of this initial question was used to guide the patient along the questionnaires on tinnitus as appropriate. Also, some patients only answered this single question and did not complete the questionnaire booklets (see results). We gave patients this option when they did not have enough time or when there was another reason for them not being able to complete the full questionnaires.

The booklets contained the following questionnaires:

- The Abbreviated Profile of Hearing Aid Benefit (APHAB - before & after implantation) is a 24-item inventory originally designed to measure the benefits that people experience from using hearing aids. It assesses the problems patients have with communication or noises in everyday situations. The inventory consists of 4 subscales: ease of communication (EC; strain of communicating under relatively favorable conditions), reverberation (RV; communicating in reverberant rooms), background noise (BN; communicating in noisy environments), and aversiveness (AV; unpleasantness of environmental sounds). Examples of items in the 4 subscales are: "When I am having

a quiet conversation with a friend, I have difficulty understanding him” (EC), “When I am talking with someone across a large empty room, I can understand the words” (RV), “I can communicate with others when we are in a crowd” (BN), “The sound of a fire engine siren close by is so loud that I need to cover my ears” (AV). On every item patients score their agreement with the item on a 7 point scale, which is afterwards transformed into a percentage score of 1-99%. Every item has to be filled in for the situation with and without the use of hearing aids [Cox and Alexander 1995]. In our population of cochlear implant recipients we asked patients to score the items before and after cochlear implantation.

- The Hospital Anxiety and Depression Scale (HADS – before & after implantation) is a 14-item assessment scale that can detect states of anxiety (7 items) and depression (7 items) in the setting of a hospital medical outpatient clinic. All items in this assessment list are answered on a 4-point scale from 0 to 3. For both the depression scale as well as the anxiety scale a score of 7 or less indicates non-cases, a score of 8-10 indicates doubtful cases and a score of ≥ 11 indicates definite cases [Zigmond and Snaith 1983].
- UMCG tinnitus questionnaire assesses tinnitus characteristics such as tinnitus sound, pitch, loudness and location. Examples of questions in the UMCG tinnitus questionnaire are: “Where do you hear your tinnitus?”, “Is your tinnitus continuous or does it come with intervals?”, “Do you perceive your tinnitus as being pulsatile?”, “At which moment of day is your tinnitus worst?”
- The Tinnitus Handicap Inventory (THI) assesses tinnitus handicap and the impact of tinnitus on everyday functioning with a 25-items scoring system in which patients answer questions about the impact of their tinnitus with yes, sometimes or no. These answers are afterwards translated with a score of 4, 2 or 0 points respectively. The total score on the THI can be calculated by adding the scores per item. A decrease of 20 points on the THI after an intervention is considered to be an indication for a successful treatment, although a recent study suggested a decrease of 7 points to be relevant [Zeman et al., 2011].
- The Tinnitus Handicap Questionnaire (THQ) measures the patients’ perceived degree of handicap due to tinnitus. Patients scored their agreement with 27 different items on a scale from 0-100 (0 = I strongly disagree, 100 = I strongly agree). The total score on the assessment list can be calculated by adding all scores together, with the scores on questions 25 and 26 being inverted, and then by dividing this score by 27 [Kuk et al., 1990, Vanneste et al., 2011].

Statistical Analysis

Results were analyzed by means of T-tests, Wilcoxon signed rank tests, univariate analyses of variance and Kruskal-Wallis tests. Normality was tested by Kolmogorov-Smirnov tests and visualized by histograms.

RESULTS

Subjects

We sent the booklets to a total number of 212 patients. A total of 182 (86%) patients responded in some way: 117 (55%) patients completed the full questionnaires, although some patients left some questions of questionnaires unanswered, 35 (17%) patients completed only the question about the change in tinnitus after cochlear implantation, and 30 (14%) patients indicated their refusal to participate (see figure 1). There was no response from the remaining 30 patients. Thus 72% of the initial 212 patients participated by completing either the full questionnaires or answering the question about tinnitus change after cochlear implantation. The main reasons for patients not to participate in the study were: a lack of time or interest, physical problems and mental problems.

Figure 1. Patient inclusion

Tinnitus changes after CI implantation

Table 1 summarizes the changes in tinnitus after cochlear implantation.

The largest group of subjects (n=45) had tinnitus neither before nor after the implantation. In the two next largest groups, tinnitus was either reduced (n=23) or was unchanged (n=22). Finally, relatively small groups experienced the onset of tinnitus (n=11), a deterioration of tinnitus (n=5), or a complete disappearance of their tinnitus (n=11). Alternatively, the data can be summarized by mentioning that of the included patients (the patients who completed the full questionnaire booklets) 52.1% reported tinnitus before implantation. In patients with pre-operative tinnitus (n=61), the change after surgery is a worsening in 8.2% and an improvement in 55.6% (tinnitus reduction or cessation). Of the patients without pre-operative tinnitus (n=56 in our sample), 19.6% (n=11) get tinnitus after surgery.

Table 1: tinnitus changes after CI implantation		
	Total	No tinnitus
before/after		
Full questionnaires + patients who only answered question about tinnitus change		
Number of patients	152	65
Percentage	100%	42.8%
Only full questionnaires		
Number of patients	117	45
Percentage	100%	38.5%
Years of tinnitus before implantation mean (SD)	18.5(14.2)	X
Years after implantation mean (SD)	4.5(2.3)	4.2(2.3)
Processor esprit3G/freedom/cp810/harmony	13/45/28/31	7/13/9/16
Tinnitus unilateral/bilateral (numbers)	23/36	X
Side of implantation numbers left/right/bilateral	50/65/2	17/28/0
Onset of tinnitus change after operation/after hearing sound	12/27	X
Phoneme scores2 mean (SD)	9.0(10.9)/57.0(21.3)**	10.4(10.3)/53.8(21.0)**
APHAB scores1 mean (SD)	71.4(16.6)/51.2(17.6)**	70.2(16.8)/51.9(16.3)**
THI scores2 mean (SD)	30.2(21.8)/22.3(20.1)*	X
THQ scores2 mean (SD)	40.4(22.1)/31.8(23.3)**	X
HADS anxiety scores2 mean (SD)	9.0(2.8)/7.8(2.5)**	8.7(2.9)/7.1(2.2)**
HADS anxiety scores ≥11 numbers	34/20	10/3
HADS depression scores2 mean (SD)	6.3(2.8)/5.3(2.2)**	6.0(2.7)/5.1(2.2)**
HADS depression scores ≥ 11 numbers	11/3	5/1

* preoperative and postoperative scores are significantly different at $P<0.05$,

** preoperative and postoperative scores are significantly different at $P<0.01$

1 paired sample t-test, 2 wilcoxon matched pair signed rank test

The number of years patients experienced tinnitus before cochlear implantation differs across the various subgroups. The group with tinnitus deterioration as well as the group with tinnitus cessation reported the largest number of years with tinnitus before implantation, respectively 26.7 years and 30.6 years. Both the group with unchanged tinnitus as well as the group with tinnitus reduction reported fewer years of tinnitus prior of implantation, respectively 13.1 and 16.4 years. On average the implantation was about 4.5 years ago. The mean years after implantation range from 4.2 years to 5.0 years in the groups of self-reported tinnitus change.

Four models of speech processors were used in the participants. A majority used a Cochlear processor (Esprit 3G, N = 13; Freedom, N = 45; CP810, N=28); the rest of the patients used an Advanced Bionics Harmony processor (N = 31). None of the patients with a positive effect of the cochlear implant on tinnitus, e.g. tinnitus reduction or tinnitus cessation after implantation, used the older Cochlear Esprit3G processor.

Tinnitus onset	Tinnitus deterioration	Unchanged tinnitus	Tinnitus reduction	Tinnitus cessation
11 7.2%	7 4.6%	29 19.1%	26 17.1%	14 9.2%
11 9.4%	5 4.3%	22 18.8%	23 19.7%	11 9.4%
X 4.7(2.9)	26.7(13.8) 5.0(3.2)	13.1(10.3) 4.6(2.3)	16.4(9.5) 4.4(2.2)	30.6(22.3) 4.8(2.8)
2/7/2/0	1/3/0/1	3/7/6/6	0/9/8/6	0/6/3/2
X 6/5/0	1/4 2/3/0	8/12 8/13/1	6/15 12/10/1	8/2 5/6/0
1/9 6.6(9.0)/41.9(27.8)	3/1 19.0(13.4)/56.9(10.5)	X 6.9(9.0)/61.1(21.8)**	3/15 7.6(10.1)/63.1(21.8)**	5/2 8.6(16.0)/63.0(20.4)**
52.5(16.9)/52.6(15.3)	72.7(15.1)/50.1(19.5)	77.6(14.0)/54.3(18.2)**	77.6(14.9)/45.0(20.0)**	75.0(13.0)/46.5(20.7)**
X/17.4(19.4)	23.4(15.9)/21.2(10.8)	27.2(23.6)/26.4(24.1)	30.6(20.2)/21.8(18.4)	44.4(21.2)/X
X/34.5(29.4)	33.9(17.2)/36.0(15.2)	37.5(23.9)/36.6(25.5)	41.2(24.6)/26.9(19.3)*	51.6(11.0)/X
7.6(2.2)/8.3(2.3)	9.0(1.0)/8.6(1.9)	9.4(3.2)/7.8(3.0)**	9.8(3.0)/8.6(2.6)	10.6(1.8)/8.4(3.0)
1/2 4.6(1.6)/5.6(2.1)*	0/1 5.8(2.2)/5.0(2.6)	8/7 6.8(3.2)/5.8(2.8)	9/5 7.0(3.4)/4.9(1.6)**	6/2 7.5(1.3)/5.3(2.3)*
0/0	0/0	3/1	3/0	0/1

Data about the side of tinnitus pre- and post-operative, the side of cochlear implantation and the start of the tinnitus change after implantation are summarized and visualized in table 1 and figure 2. Not all patients answered these questionnaires, so only the data of 106 patients could be presented. Overall more patients report bilateral tinnitus than unilateral tinnitus. An exception is the group with tinnitus cessation after implantation. In this group 8 patients report unilateral tinnitus and only 2 patients report bilateral tinnitus.

In the patients who experienced the start of tinnitus after implantation (see figure 2A), tinnitus occurred most of the times at the side of the implanted ear and in a smaller group the tinnitus occurred bilateral. In the patients who experienced unilateral tinnitus before implantation (see figure 2B), the majority did not experience tinnitus anymore after implantation. As can be seen from the hatched area in the figure in most of these patients the cochlear implant was implanted at the side of the monaural preoperative tinnitus. Concerning the patients with preoperative bilateral tinnitus (see figure 2C) a group of patients experienced tinnitus cessation or experienced that their tinnitus turned to a unilateral tinnitus after implantation (n=16). However 14 patients reported that their tinnitus remained bilateral after implantation.

Figure 2. Lateralization of tinnitus after cochlear implantation. The results are grouped with respect to the pre-operative tinnitus lateralization: (a) no pre-op tinnitus, (b) unilateral pre-op tinnitus, (c) bilateral pre-op tinnitus. For each pre-op lateralization condition, the number of patients is indicated with (1) tinnitus ipsilateral to the surgery side, (2) bilateral tinnitus, (3) tinnitus contralateral to the surgery side, and (4) no post-op tinnitus. The hatched areas correspond to patients with monaural pre-op tinnitus and surgery on the pre-op tinnitus side. The red color indicates patients that noticed a change in their tinnitus immediately after the surgery.

In table 1 is visualized that the effect on tinnitus lateralization after implantation can occur immediately after surgery as well as later in the rehabilitation period. Overall twelve patients remembered their tinnitus had changed immediately after the surgery. In contrast, 27 patients answered that they experienced the difference in tinnitus after hearing sound with their cochlear implant. Sixty-seven patients could not remember when their tinnitus changed.

For the total group of patients, our analyses showed significant improvements in the postoperative phoneme scores ($P < 0.01$). This means that speech understanding was better after implantation. Concerning the different groups of self-reported tinnitus change, all groups showed post-operative improvements in speech understanding.

Similar results were found for the APHAB questionnaire. Overall patients scored significantly lower on the APHAB after implantation compared to the situation before implantation ($P < 0.01$). This means that the patients reported less limitations in daily life as a consequence of their hearing loss after implantation. Also here, only the groups that reported a negative effect of cochlear implantation on tinnitus, i.e. tinnitus onset or deterioration, did not show significant differences between pre- and post-operative APHAB scores.

For the entire group of patients the mean postoperative scores on the THQ and THI were significantly lower compared to the mean postoperatively collected preoperative scores on these questionnaires (respectively $P < 0.01$ and $P < 0.05$). This means that overall patients experienced less limitations due to their tinnitus after implantation compared to the situation before implantation. This is also shown in figure 3 and 4. Figure 3 is a boxplot in which the mean scores and the standard deviations on the THI and THQ before and after implantation are shown. Figure 4 is a scatter plot in which the scores before and after implantation on the THI and THQ are coupled per subject. Figure 4 shows that besides lowering of the mean score on the THI and THQ after implantation also the majority of individual patients experience less tinnitus handicap after cochlear implantation. In these figures the scores of the patients with tinnitus onset and tinnitus cessation are left out, because these patient filled in the tinnitus handicap questionnaires only once. For five of the groups the changes in the mean scores on the THI and THQ after implantation were consistent with the self-reported tinnitus change as perceived by the patients. This means for example that the group that reported tinnitus reduction after implantation also showed a lowering in the mean THI/THQ score after implantation. Only, the patients who reported a deterioration of tinnitus after the cochlear implantation did not show higher mean scores

Figure 3. Boxplot of mean scores and standard deviations on THI and THQ before and after cochlear implantation

Figure 4. Scatterplot of mean score per patient on THI and THQ before and after cochlear implantation

on the THI and THQ after implantation. The mean preoperative and postoperative scores on these questionnaires were not significantly different in this group, which means that these patients experienced approximately the same amount of limitations due to tinnitus before and after implantation. In most groups the THQ showed larger changes comparing preoperative and postoperative scores than the THI.

On average patients showed both before and after implantation moderate scores on the HADS anxiety questions and low scores on the HADS depression questions. Only the groups that reported tinnitus reduction or tinnitus cessation after implantation also reported moderate scores on the HADS depression questions before implantation. The mean HADS scores both on anxiety and depression after implantation for the total group of patients were significantly lower than the mean scores before implantation (for both scores $P < 0.01$). Thus, on average patients reported less symptoms of anxiety and depression after implantation. Only the group that reported tinnitus onset after implantation showed higher mean scores on anxiety and depression after implantation. Concerning HADS scores ≥ 11 , i.e. scores that indicate cases likely of a clinical depression or anxiety, one can see that overall the amount of patients with these high scores is reduced after cochlear implantation. Of the patients that report a positive effect of their cochlear implant on tinnitus (tinnitus cessation or tinnitus reduction) the amount of patients with high anxiety scores reduces after implantation, while in the groups that report a negative effect of the cochlear implant on their tinnitus (tinnitus deterioration or tinnitus onset) the amount of patients with high anxiety scores increases after implantation. Concerning high depression scores this trend is not noticeable.

DISCUSSION

In this study we retrospectively studied tinnitus in a group of cochlear implant recipients, before and after the implantation. In the largest group of subjects (49%) tinnitus was present neither before nor after cochlear implantation. In the majority of subjects preoperative tinnitus either remained unchanged (19%), diminished (20%) or stopped (9%). Finally, in a small group new tinnitus emerged after the surgery (9%), or the existing tinnitus got worse (4%). Besides, our results showed that across the entire group the hearing handicap and the tinnitus handicap decreased, and signs of anxiety or depression also decreased. These effects depended on the change that subjects experienced on their tinnitus, as was shown in the analysis where subjects were stratified with respect to the change of tinnitus after the surgery (Table 1).

In line with previous reports, the prevalence of tinnitus in cochlear implant candidates and recipients confirms that tinnitus is a frequent phenomenon in this population. This prevalence is higher than the 10-15% in a general population and even higher than in the hearing impaired population [Arts et al., 2012]. It is estimated that the prevalence of tinnitus is about three times higher in those with impaired hearing than in those with normal hearing [Holmes and Padgham 2011]. Nevertheless, the prevalence of tinnitus in our study cohort is somewhat lower than the 67-100% range that was reported in earlier studies on tinnitus in cochlear implant recipients [Kompis et al., 2012, Quaranta et al., 2008, Baguley and Atlas 2007]. It has been suggested that the reason for a difference in prevalence could be the shift in candidacy criteria for cochlear implantation [Baguley and Atlas 2007]. Most papers about the prevalence of tinnitus in cochlear implant candidates were published from 1990 to 2006, which may have been associated with a higher prevalence of tinnitus. In contrast, our subjects were implanted between 2000 and 2009.

None of the subjects in our studies received a cochlear implant for tinnitus suppression. Instead, the primary goal of implantation was to treat profound hearing and to improve the ability to understand speech. This was obviously successful, as the phoneme score showed a marked increase following implantation (table 1). The improvement of the average phoneme score was observed in all subgroups, regardless of the change in tinnitus. However, this improvement was not significant in the subjects that had experienced an onset or a deterioration of tinnitus, which is likely due to the small size of these subgroups. The improvement in speech understanding was mirrored by a marked hearing aid benefit (measured by the APHAB questionnaire). However, in the subjects that had an onset of tinnitus, the benefit was not present. This presumably reflects the fact that in these subjects the tinnitus interferes with their ability to communicate.

Our study was unique in that it used two questionnaires to assess tinnitus handicap. Both questionnaires (THI and THQ) showed relatively mild tinnitus handicap, both before and after implantation. The effect of implantation on these handicap scores was also relatively mild, and reached statistical significance only for the THQ in the group that had a reduction of tinnitus. Even in the group that showed a deterioration of tinnitus after implantation, the tinnitus handicap scores only mildly changed. The largest tinnitus handicap scores were observed in the subjects that had a cessation of their tinnitus. These patients gave the highest retrospective score of the pre-operative tinnitus. This may be due to response shift, as is discussed below. No big differences were found between the overall scores on the THI and THQ. In the five groups of self reported tinnitus change the THQ seems to

give some bigger changes between the preoperative and postoperative scores, while the standard deviations are almost the same for both questionnaires._

The signs of anxiety and depression mildly reduced by cochlear implantation, except in the subjects that had an onset of tinnitus [Andersson et al., 2009]. In the latter subjects, the average anxiety and depression scores slightly increased, which was statistically significant for depression. In the other subgroups, the change in anxiety and depression does not have an obvious relation with the change in tinnitus. This may indicate that the mild changes in these scores are not related to tinnitus, but probably more so to the improvement of the ability to hear.

Side of implantation

A key hypothesis in the pathogenesis of subjective tinnitus is that it arises as a response of the central auditory system to peripheral hearing loss. Peripheral hearing loss results in a decrease of afferent input to the brainstem. This may result in a change of spontaneous neural activity in the central auditory system, which is believed to potentially cause tinnitus. Cochlear implantation may attenuate tinnitus, as is obvious from several previous reports on the effect of hearing rehabilitation on tinnitus, possibly due to the restoration of afferent input to the brainstem [Quaranta et al., 2008, Baguley and Atlas 2007, Bovo et al., 2010]. It would be expected that one-sided cochlear implantation would decrease tinnitus in the implanted ear. Thus, if an implant is placed in the tinnitus ear in a patient with unilateral tinnitus, it would be expected to reduce the tinnitus. However, due to the central processing of bilateral sounds, tinnitus may be perceived unilaterally, simply because it is louder in one ear. Then, implantation in the tinnitus ear may cause the tinnitus to shift to the contralateral ear. In our patient group we observed both types of tinnitus change: in some patients tinnitus disappeared after implanting the tinnitus ear, in one patient tinnitus moved to the contralateral ear and in a number of patients with bilateral tinnitus, the tinnitus moved to the contralateral ear.

Unfortunately, in some patients tinnitus occurred or deteriorated on the implantation side. In such cases it has been suggested that the insertion trauma may have caused the change in tinnitus [Kompis et al., 2012, Baguley and Atlas 2007, Bovo et al., 2010]. Our observation that 12 of the 49 patients noted a change of their tinnitus immediately after implantation seems to support that electrode insertion in the cochlea could play a role in tinnitus changes after cochlear implantation. Note that five of these 12 subjects noted a cessation of their tinnitus immediately after surgery. Apparently, insertion of the electrode in the cochlea could also have positive effects on tinnitus. It is anticipated that further

development of atraumatic electrode insertion may reduce effects that recipients observe immediately after the surgery [Adunka et al., 2010].

Response bias

For this questionnaire study we used a retrospective design, which is also referred to as the ‘thentest’. There are two important disadvantages of this design, the first of which is related to the time between implantation and the questionnaires completion, which mount up to 10 years in our study. This long recall interval may incur recall bias, which is caused by the fact that patients may not remember the situation before the intervention very well at the time the questionnaires are filled in. This could magnify the effects: for example patients with a positive effect of implantation on tinnitus may remember the situation before implantation worse than it actually was resulting in an overestimation of the positive effect of cochlear implantation. Second, there is potential contamination due to social desirability and effort justification, causing a tendency for patient to wanting to fulfill our expectation. This may enhance the apparent positive effect of cochlear implantation. Thus, the recall bias and the desirability bias could be in favour of a positive effect of cochlear implantation on tinnitus.

However, the retrospective design also has one major benefit: there is no response shift. Response shift refers to the phenomenon that people tend to change their internal standards or values of how they function, for example with respect to their quality of life, after they experienced changes in health [Schwartz et al., 2006]]. Normally, people adapt to the impairments they have, such as hearing loss. After something has changes in their health situation (for example after CI implantation), they function at a new (higher) level, which causes to re-evaluate their health situation and reset the internal standard of their health condition. Response shift can affect the results of questionnaire studies with a ‘pretest-posttest’ design, since the questionnaires are filled in at different times. The adaptational processes between both assessments times can cause changes in patients’ quality of life evaluations [Visser et al., 2005]], thereby giving an underestimation of the change between pre- and posttest [Schwartz et al., 2006]]. Such changes cannot occur in the retrospective design used here, because all assessments are performed at one point in time.

In summary, both study designs have advantages and disadvantages. The retrospective (thentest) and prospective (pretest-posttest) may have an different effect on the magnitude of the effect of an intervention, respectively. While the retrospective design may overestimate this effect, the prospective design may underestimate the effect. It thus

is useful to evaluate the effect of a treatment by a combination of both approaches, in order to estimate the effect of treatment.

CONCLUSION

Summarized, the prevalence of tinnitus in cochlear implant patients is relatively high. In these patients the tinnitus severity is generally mild to moderate. Cochlear implantation reduces tinnitus in an important part of the patients, but has a negative influence on tinnitus in some patients. However, in the patients who show tinnitus deterioration the tinnitus handicap does not increase and in the patients who show tinnitus onset after implantation the tinnitus handicap is mild. Cochlear implantation has a mildly positive effect on anxiety and depression, which is most likely due to improvement of the hearing ability.

REFERENCES

- Adunka OF, Pillsbury HC, Buchman CA: Minimizing intracochlear trauma during cochlear implantation. *Adv.Otorhinolaryngol.* 2010;67:96-107.
- Akdogan O, Ozcan I, Ozbek C, Dere H: Tinnitus after cochlear implantation. *Auris Nasus Larynx* 2009;36:210-212.
- Andersson G, Freijd A, Baguley DM, Idrizbegovic E: Tinnitus distress, anxiety, depression, and hearing problems among cochlear implant patients with tinnitus. *J.Am.Acad.Audiol.* 2009;20:315-319.
- Andersson G, Stromgren T, Strom L, Lyttkens L: Randomized controlled trial of internet-based cognitive behavior therapy for distress associated with tinnitus. *Psychosom.Med.* 2002;64:810-816.
- Arts RA, George EL, Stokroos RJ, Vermeire K: Review: cochlear implants as a treatment of tinnitus in single-sided deafness. *Curr.Opin.Otolaryngol.Head Neck Surg.* 2012;20:398-403.
- Baguley DM, Atlas MD: Cochlear implants and tinnitus. *Prog.Brain Res.* 2007;166:347-355.
- Berliner KI, Shelton C, Hitselberger WE, Luxford WM: Acoustic tumors: effect of surgical removal on tinnitus. *Am.J.Otol.* 1992;13:13-17.
- Bovo R, Ciorba A, Martini A: Tinnitus and cochlear implants. *Auris Nasus Larynx* 2010;.
- Cox RM, Alexander GC: The abbreviated profile of hearing aid benefit. *Ear Hear.* 1995;16:176-186.
- Eggermont JJ, Komiya H: Moderate noise trauma in juvenile cats results in profound cortical topographic map changes in adulthood. *Hear.Res.* 2000;142:89-101.
- Eggermont JJ, Roberts LE: The neuroscience of tinnitus. *Trends Neurosci.* 2004;27:676-682.
- Holmes S, Padgham ND: "Ringing in the ears": narrative review of tinnitus and its impact. *Biol. Res.Nurs.* 2011;13:97-108.
- Holmes S, Padgham ND: Review paper: more than ringing in the ears: a review of tinnitus and its psychosocial impact. *J.Clin.Nurs.* 2009;18:2927-2937.
- House WF: Cochlear implants. *Ann.Otol.Rhinol.Laryngol.* 1976;85 suppl 27:1-93.
- Kaltenbach JA: Neurophysiologic mechanisms of tinnitus. *J.Am.Acad.Audiol.* 2000;11:125-137.
- Kiang NY, Moxon EC, Levine RA: Auditory-nerve activity in cats with normal and abnormal cochleas. In: *Sensorineural hearing loss. Ciba Found.Symp.* 1970;241-273.
- Kim DK, Bae SC, Park KH, Jun BC, Lee DH, Yeo SW, Park SN: Tinnitus in patients with profound hearing loss and the effect of cochlear implantation. *Eur.Arch.Otorhinolaryngol.* 2012;.
- Knutson JF, Murray KT, Husarek S, Westerhouse K, Woodworth G, Gantz BJ, Tyler RS: Psychological change over 54 months of cochlear implant use. *Ear Hear.* 1998;19:191-201.
- Kompis M, Pelizzone M, Dillier N, Allum J, Demin N, Senn P: Tinnitus before and 6 Months after Cochlear Implantation. *Audiol.Neurotol.* 2012;17:161-168.
- Kuk FK, Tyler RS, Russell D, Jordan H: The psychometric properties of a tinnitus handicap questionnaire. *Ear Hear.* 1990;11:434-445.

- Lockwood AH, Salvi RJ, Burkard RF: Tinnitus. *N.Engl.J.Med.* 2002;347:904-910.
- Mo B, Lindbaek M, Harris S: Cochlear implants and quality of life: a prospective study. *Ear Hear.* 2005;26:186-194.
- Moller AR: Pathophysiology of tinnitus. *Ann.Otol.Rhinol.Laryngol.* 1984;93:39-44.
- Olze H, Szczepek AJ, Haupt H, Forster U, Zirke N, Grabel S, Mazurek B: Cochlear implantation has a positive influence on quality of life, tinnitus, and psychological comorbidity. *Laryngoscope* 2011;121:2220-2227.
- Pan T, Tyler RS, Ji H, Coelho C, Gehringer AK, Gogel SA: Changes in the tinnitus handicap questionnaire after cochlear implantation. *Am.J.Audiol.* 2009;18:144-151.
- Preece JP, Tyler RS, Noble W: The management of tinnitus. *Geriatr. Aging* 2003;6:22-28.
- Quaranta N, Fernandez-Vega S, D'elia C, Filipo R, Quaranta A: The effect of unilateral multichannel cochlear implant on bilaterally perceived tinnitus. *Acta Otolaryngol.* 2008;128:159-163.
- Roberts LE, Eggermont JJ, Caspary DM, Shore SE, Melcher JR, Kaltenbach JA: Ringing ears: the neuroscience of tinnitus. *J.Neurosci.* 2010;30:14972-14979.
- Rubinstein JT, Tyler RS, Johnson A, Brown CJ: Electrical suppression of tinnitus with high-rate pulse trains. *Otol.Neurotol.* 2003;24:478-485.
- Schwartz CE, Bode R, Repucci N, Becker J, Sprangers MA, Fayers PM: The clinical significance of adaptation to changing health: a meta-analysis of response shift. *Qual.Life Res.* 2006;15:1533-1550.
- Silverstein H: Transmeatal labyrinthectomy with and without cochleovestibular neurectomy. *Laryngoscope* 1976;86:1777-1791.
- Stouffer JL, Tyler RS: Characterization of tinnitus by tinnitus patients. *J.Speech Hear.Disord.* 1990;55:439-453.
- Tyler RS: Does tinnitus originate from hyperactive nerve fibers in the cochlea? *J. LARYNGOL. OTOL.* 1983;97:38-44.
- Tyler RS, Baker LJ: Difficulties experienced by tinnitus sufferers. *J.Speech Hear.Disord.* 1983;48:150-154.
- Van de Heyning P, Vermeire K, Diebl M, Nopp P, Anderson I, De Ridder D: Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation. *Ann.Otol.Rhinol.Laryngol.* 2008;117:645-652.
- Vanneste S, To WT, De Ridder D: The psychometric properties of the Tinnitus Handicap Questionnaire in a Dutch-speaking population. *Clin.Otolaryngol.* 2011;36:9-16.
- Visser MR, Oort FJ, Sprangers MA: Methods to detect response shift in quality of life data: a convergent validity study. *Qual.Life Res.* 2005;14:629-639.
- Wang J, Salvi RJ, Powers N: Plasticity of response properties of inferior colliculus neurons following acute cochlear damage. *J.Neurophysiol.* 1996;75:171-183.
- Zeman F, Koller M, Figueiredo R, Azevedo A, Rates M, Coelho C, Kleinjung T, de Ridder D,

- Langguth B, Landgrebe M: Tinnitus handicap inventory for evaluating treatment effects: which changes are clinically relevant? *Otolaryngol.Head.Neck.Surg.* 2011;145:282-287.
- Zigmond AS, Snaith RP: The hospital anxiety and depression scale. *Acta Psychiatr.Scand.* 1983;67:361-370.
- Zoger S, Svedlund J, Holgers KM: Psychiatric disorders in tinnitus patients without severe hearing impairment: 24 month follow-up of patients at an audiological clinic. *Audiology* 2001;40:133-140.

4

MODELS TO PREDICT POSITIVE AND NEGATIVE EFFECTS OF COCHLEAR IMPLANTATION ON TINNITUS

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ABSTRACT

Objectives

The effect of cochlear implantation on tinnitus is heterogeneous: implantation does not always reduce tinnitus and may even worsen tinnitus. Therefore, it is important to know which factors influence the consequences of cochlear implantation for tinnitus. To date, no consensus has been reached regarding the factors that influence tinnitus. This study aimed to create prognostic models, using binary logistic regression analyses to predict positive or negative changes in tinnitus after cochlear implantation.

Methods

For this study we retrospectively sent two questionnaire packages to 117 cochlear implant patients.

Results

In the binary logistic regression analyses of the responses to the questionnaires, it was not possible to create a significant model to predict a positive effect of cochlear implantation on tinnitus. However, a negative effect of cochlear implantation on tinnitus was predictable, using a backward stepwise selection method in a model including the APHAB (Abbreviated Profile of Hearing Aid Benefit) and THQ (Tinnitus Handicap Questionnaire) ($p < 0.001$, Nagelkerke $R^2 = 0.529$).

Conclusions

Our results suggest that the lower the preoperative tinnitus handicap and the preoperative hearing handicap, the higher the chance that cochlear implantation will worsen tinnitus. More research needs to be done, preferable in a big prospective study, to make this model instrumental for clinical decision making and pre-operative patient counselling. However, our results might suggest that preoperative THQ and APHAB screening could be meaningful. Especially in patients who are afraid to develop tinnitus or tinnitus worsening as complication of cochlear implantation.

INTRODUCTION

Recently, some medical centers have started using cochlear implantation as a treatment for tinnitus in patients with single-sided deafness (Van De Heyning et al., 2008). Since cochlear implantation does not always reduce tinnitus, and may even have deleterious effects, it is important to know which factors influence the outcome of cochlear implantation on tinnitus. Previous studies describing the factors influencing the outcome of cochlear implantation on tinnitus did not show consistent results, and in some even contrary outcomes were reported.

Some factors have been reported to predict a positive effect of cochlear implantation on tinnitus. These include: higher preoperative tinnitus handicap scores, especially higher scores on the emotional subscale of tinnitus handicap questionnaires (Olze, Szczepek, Haupt, Förster, et al., 2011; Olze, Szczepek, Haupt, Zirke, et al., 2011; Pan et al., 2009; Souliere, Kileny, Zwolan, & Kemink, 1992), a higher age at implantation, higher preoperative hearing handicap scores (Amoodi et al., 2011), higher preoperative stress levels (Olze, Szczepek, Haupt, Förster, et al., 2011; Olze, Szczepek, Haupt, Zirke, et al., 2011), as well as fewer years of hearing loss (Olze, Szczepek, Haupt, Förster, et al., 2011; Olze, Szczepek, Haupt, Zirke, et al., 2011). However, a relationship between age at implantation, the number of years of tinnitus before implantation, and the level of hearing loss before implantation could not consistently be confirmed as exerting a positive effect of implantation on tinnitus (Kompis et al., 2012).

In cochlear implant candidates who receive their implant because of severe hearing loss, besides being able to predict a positive effect of cochlear implantation on tinnitus, it is also important to be able to predict a negative effect, i.e. deterioration or the onset of tinnitus after implantation. Knowing negative predictive factors might help clinicians in their preoperative counselling on the risks of developing tinnitus after the operation. Previous studies suggest that a higher age at implantation, higher preoperative tinnitus handicap scores (Pan et al., 2009), better hearing before implantation, a shorter period of hearing loss before implantation, higher additional hearing loss after implantation and worse phoneme scores after implantation correlate with a negative effect of implantation on tinnitus. However, most of these correlations lack statistical significance (Kompis et al., 2012).

Since there is no clear evidence concerning which factors reliably predict the effects of cochlear implantation, we created models predicting positive or negative changes in tinnitus after implantation.

MATERIAL AND METHODS

The present study describes logistic regression analyses of data that were reported in an earlier paper by Klooststra et al. (Klooststra, Arnold, Hofman, & Van Dijk, 2015). As that paper extensively described, patients who received a cochlear implant between 2000 and 2009 in the University Medical Center Groningen in the Netherlands were recruited for the study. All surgeries were performed by two neuro-otological surgeons who were experienced in a wide range of ear surgeries, including in particular cochlear implantation. A majority of patients (n=86) were implanted with a cochlear implant of the firm 'Cochlear' (implant type CI24RE or CI422), the other 31 patients were implanted with the cochlear implant of the firm 'Advanced Bionics'. There was full insertion of the electrode in all patients and all electrodes were inserted by a round window insertion. Only with the CI24RE and the Advanced Bionics implants the round window was enlarged using a small drill. The patients with an implant of the firm 'Cochlear' used the following speech processors: Esprit 3G, N = 13; Freedom, N = 45; CP810, N=28. The patients with an implant of the firm 'Advanced Bionics' used the Harmony speech processor (N=31). All patients older than 18 years of age who had used their cochlear implant for at least six months were approached for inclusion. A few months to several years after they were implanted, a total of 117 patients retrospectively and simultaneously filled in two questionnaire booklets. Booklet one contained a number of questionnaires concerning the situation before implantation and booklet two the situation after implantation. Patients who did not experience tinnitus before and/or after implantation did not fill in the questionnaires concerning a tinnitus handicap.

The principal question of the questionnaire booklets was: 'Were there any changes concerning your tinnitus after the cochlear implantation?'. Possible responses were: A) No, I did not experience tinnitus before and after implantation; B) No, my already existing tinnitus remained the same after implantation; C) Yes, I started to experience tinnitus after implantation; D) Yes, my already existing tinnitus got worse after implantation; E) Yes, my already existing tinnitus got better after implantation; F) Yes, the tinnitus I experienced before implantation disappeared after implantation. In addition, the two booklets contained a number of standardized questionnaires: 1) The Abbreviated Profile of Hearing Aid Benefit (APHAB) (Cox & Alexander, 1995), 2) The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983), 3) UMCG tinnitus questionnaire, 4) The Tinnitus Handicap Inventory (THI) (Newman, Jacobson, & Spitzer, 1996; Zeman et al., 2011), 5) The Tinnitus Handicap Questionnaire (THQ) (Kuk, Tyler, Russell, & Jordan, 1990; Vanneste, To, & De Ridder, 2011), 6) The type D-Scale (DS14) (Denollet, 2005), and 7) The Life Orientation Test (LOT) (Scheier & Carver, 1985).

Apart from the questionnaire booklets, information about audiological tests and the date of implantation was gathered from the patients' clinical files.

The study was approved by the Medical Ethics Committee of the University Medical Hospital Groningen. Before participation, all patients gave their written informed consent.

Statistical Analysis

In order to create a prognostic model, we used the question about the presence of tinnitus pre- and post-surgery as the dependent outcome factor (table 1).

Table 1: regrouping dependent outcome factor

Patients with positive effect	Patients without positive effect
Answers E+F (23+11=34)	Answers B+D (22+5=27)
Patients with negative effect	Patients without negative effect
Answers C+D (11+5=16)	Answers A+B+E+F (45+22+23+11=101)

We classified patients as having a positive effect of cochlear implantation on tinnitus when they answered this question with E) 'my already existing tinnitus got better after implantation' and F) 'the tinnitus I experienced before implantation disappeared after implantation'. The model to predict a positive effect of implantation can, of course, only be assessed in patients that experienced tinnitus prior to surgery. Hence, 61 out of 117 patients were included in the analyses of a positive effect of implantation on tinnitus. Within this group of patients, we compared the subgroup who experienced a positive effect of implantation on their tinnitus with the subgroup who did not experience a positive effect of the implantation.

Of the 61 patients included with preoperative tinnitus, 34 patients experienced a positive effect of implantation on their tinnitus, i.e. suppression or cessation of tinnitus after cochlear implantation.

We classified patients as having a negative effect of cochlear implantation on tinnitus when they answered the question with C) 'I started to experience tinnitus after implantation' and D) 'my already existing tinnitus got worse after implantation'. In order to predict which cochlear implant candidates had more chance of a negative effect of implantation on

tinnitus, we included all 117 patients that completed the questionnaires in the analyses, because we wanted to know from the whole group of operated patients which type of patient experienced a negative outcome of implantation on tinnitus. Of 117 patients, 16 experienced a negative effect on their tinnitus, i.e. a worsening of tinnitus (n=5) or onset (n=11) of tinnitus after implantation.

Based on previous studies and our own expectations, we included the following continuous pre-operative predictors in our analysis: tinnitus handicap (THI and THQ), personality characteristics (social inhibition, negative affect (DS14), optimism (LOT)), anxiety and depression (HADS), hearing handicap (APHAB), pre-operative speech comprehension scores, mean pre-operative hearing loss in decibels, years of tinnitus before implantation, and the age at the time of inclusion. To test which factors could be relevant as predictors, we first analyzed the factors by means of t-tests (THI, PTA of 1000Hz/2000Hz/4000Hz, APHAB) or Mann Whitney U-tests (THQ, HADS-depression, HADS-anxiety, DS14-negative affectivity, DS14-social inhibition, LOT, phoneme scores, age at inclusion and years of preoperative tinnitus), dependent on whether the variables were normally distributed or not. With these t-tests and Mann Whitney U-tests, we tested whether there was a relevant difference in the scores for these factors between the positive effect group and the no effect+negative effect group. In addition, we tested if there was a relevant difference in the scores between the negative effect group and the no effect group+positive effect group, since this may identify this factor as a predictor of the postoperative effect. As a rule of thumb, we included variables in the subsequent logistic regression analysis if the corresponding difference was significant at $p < 0.25$.

For statistical analyses we used IBM SPSS statistics 20.

RESULTS

Positive effect of cochlear implantation on tinnitus

A total of 61 of 117 patients were included in the logistic model for a positive effect of implantation on tinnitus. The initial analysis (table 2) revealed relevant differences ($p < 0.25$) in THI and DS-14 negative affectivity scores between patients with and without a positive effect of implantation on tinnitus. Therefore, we considered these variables to be potential predictors of a positive effect of implantation on tinnitus. Binary logistic analyses with these variables as predictors in the model identified neither THI-scores nor DS14-negative affectivity as a significant predictor of a positive effect of implantation on tinnitus. The lack of significance was observed when including both THI and the DS14-

Table 2: p-values of the difference in means of patients with or without a positive effect of CI on tinnitus

T-tests	p-values	Mean patients with positive effect (N=34)	Mean patients without positive effect (N=27)
THI	.142	34.94	26.45
APHAB	.979	76.73	76.63
Mean dB hearing loss	.656	105.69	104.08
Mann-Whitney U tests			
THQ	.268	43.89	36.75
DS14 Negative affectivity	.082	13.00	10.12
DS14 Social inhibition	.844	12.88	12.84
LOT	.853	20.44	20.24
years of tinnitus	.429	25.38	21.89
Phonemescores	.358	7.93	9.30
Age at inclusion	.366	61.35	64.54
HADS-anxiety	.428	9.88	9.32
HADS-depression	.333	7.16	6.56

negative affectivity in the model (THI + DS14-negative affectivity: $p=0.239$, Nagelkerke $R^2 = 0.066$) and when these variables were included separately (THI: $p=0.133$, Nagelkerke $R^2 = 0.051$; DS14-negative affectivity: $p=0.096$, Nagelkerke $R^2 = 0.063$).

Negative effect of cochlear implantation on tinnitus

All 117 patients were included in the logistic model for a negative effect of implantation on tinnitus. The initial analysis (table 3) found relevant differences ($p<0.25$) between patients with and without a negative effect of CI in tinnitus for the variables: THI, THQ, APHAB, DS14-negative affectivity, DS14-social inhibition, HADS-anxiety and HADS-depression.

Therefore, these variables were considered to be potential predictors of a negative effect of implantation. In a first binary logistic analysis, we included all of these variables and

Table 3: p-values of the difference in means of patients with or without a negative effect of CI on tinnitus

T-tests	p-values	Mean patients with negative effect (N=16)	Mean patients without negative effect (N=101)
THI	.000	8.34	31.87
APHAB	.001	58.82	73.95
Mean dB hearing loss	.981	105.83	105.74
Mann-Whitney U tests			
THQ	.000	10.60	41.15
DS14 Negative affectivity	.049	6.69	10.18
DS14 Social inhibition	.002	8.38	12.77
LOT	.871	20.69	20.34
years of tinnitus	.371	31.33	23.31
Phonemescores	.419	11.35	8.75
Age at inclusion	.739	59.00	62.87
HADS-anxiety	.173	8.06	9.24
HADS-depression	.030	4.94	6.52

Table 4: binary logistic regression analysis of negative effect of CI on tinnitus (all variables included)

Variable	B	Standard Error	Significance (Wald)	Exp (B)	95% Confidence Interval
THI	-0.027	0.046	0.552	0.973	0.890-1.064
THQ	-0.027	0.038	0.488	0.974	0.903-1.050
DS14-na	0.029	0.096	0.761	1.030	0.854-1.242
DS14-si	-0.165	0.104	0.113	0.848	0.691-1.040
APHAB	-0.065	0.029	0.027	0.937	0.885-0.992
HADS-a	-0.094	0.203	0.644	0.911	0.612-1.355
HADS-d	-0.127	0.208	0.541	0.880	0.585-1.324

(p<0.001, Nagelkerke $R^2 = 0.559$)

identified a significant model (p<0.001, Nagelkerke $R^2 = 0.559$) (table 4). However, not all individual variables in this model were significant predictors of a negative effect. We thus performed a backward stepwise selection method to create a more reliable model. We removed a variable from our model if the p-value on the Wald statistic and the significance of change of the likelihood ratio was >0.05. Based on this, we included only the APHAB and the THQ in our final model. With these variables, we created a model with a significance of p<0.001 and a Nagelkerke R^2 of 0.529 (table 5). Both THQ (p=0.004 Wald statistic, p=0.001 Likelihoodratio) and APHAB (p=0.031 Wald statistic, p=0.026 Likelihoodratio) were each significantly related to a negative effect of implantation on tinnitus. The relation of the THQ with a negative of implantation on tinnitus is only relevant for patients with tinnitus deterioration after implantation and not relevant for patients with tinnitus onset after implantation because these last patients did not fill in the preoperative THQ. Our model indicates that the lower the preoperative tinnitus handicap (B=-0.056) and the lower the preoperative hearing handicap (B=-0.070), the higher the chance a patient has of experiencing a negative effect of cochlear implantation on tinnitus.

Table 5: binary logistic regression analysis of negative effect of CI on tinnitus (reduced model)

Standard Error	Significance (Wald)	Exp (B)	95% Confidence Interval
0.024	0.004	0.933	0.890-0.977
0.026	0.031	0.946	0.899-0.995

(p<0.001, Nagelkerke $R^2 = 0.529$)

Our model fulfilled all assumptions for logistic regression analysis. We tested the linearity of the logit of the model and found that none of the interaction terms were significant (THQ x LnTHQ p=0.305, APHAB x LnAPHAB p=0.736). This indicates that the assumption

Table 6: Collinearity Statistics

	Tolerance	VIF
THQ	0.888	1.126
APHAB	0.888	1.126

of linearity of the logit had been met. We tested multicollinearity by tolerance- and VIF-values. All tolerance values were larger than 0.1 and all VIF values were smaller than 10, which makes multicollinearity unlikely (see table 6).

DISCUSSION

Because the predictors of the effect of cochlear implantation on tinnitus were unclear, in this study we created prognostic models for positive and negative changes in tinnitus after cochlear implantation.

Unfortunately, we could not create a well-fitted model to predict a positive effect on tinnitus in patients with preoperative tinnitus. In contrast, for the negative effects of cochlear implantation on tinnitus, predictors could be established. The strongest predictors for a negative effect of cochlear implantation were a low preoperative tinnitus handicap and a low preoperative hearing handicap.

With regard to a positive effect of cochlear implantation on tinnitus, we could not confirm the results from previous studies in which the years of hearing loss, higher preoperative hearing handicap scores, higher preoperative tinnitus handicap scores and a higher age at implantation predicted better effects of cochlear implantation on tinnitus (Amoodi et al., 2011; Kompis et al., 2012; Olze, Szczepek, Haupt, Förster, et al., 2011; Olze, Szczepek, Haupt, Zirke, et al., 2011; Pan et al., 2009; Souliere et al., 1992). Most likely this is due to there being other factors involved in the effect of cochlear implantation on tinnitus that we did not include in our models. Higher preoperative tinnitus handicap scores as a predictor in previous studies could also be explained by the ‘regression toward the mean’ principle, i.e. if the tinnitus handicap is extreme on its first measurement (before cochlear implantation), it will tend to be closer to the average on its second measurement (after cochlear implantation).

Concerning the negative effect of cochlear implantation on tinnitus, the strongest predictors in the binary logistic model were the preoperative tinnitus handicap and the preoperative hearing handicap.

A low preoperative tinnitus handicap (only relevant for patient with preoperative tinnitus) score as a predictor of a negative effect on tinnitus is consistent with our expectations. This outcome could be explained by the fact that the less handicap patients experience before

the operation, the greater the chance that the postoperative outcome is disappointing. Besides, in patients with a high level of tinnitus handicap, the physiology of the brain can be changed due to the changed pattern of spontaneous activity of the neural system that occurs in tinnitus (Eggermont & Roberts, 2004). Possibly, this makes the brain of these patients less sensitive to (negative) changes in tinnitus after cochlear implantation, in contrast to patients with a low tinnitus handicap in whom these changes in the physiology of the brain have not (yet) occurred.

The result that a lower hearing handicap predicts a negative effect on tinnitus also confirms our expectations. This outcome could also be explained by same mechanisms as described above with a greater tinnitus handicap.

Our results concerning hearing handicap are in agreement with those described before by Kompis et al. (Kompis et al., 2012) who describe that patients that develop tinnitus postoperatively had slightly better preoperative hearing thresholds in the implanted ear.

Also, some studies describe a positive relationship between the amount of hearing handicap and the amount of tinnitus distress a patient experiences (Amoodi et al., 2011; Andersson, Freijd, Baguley, & Idrizbegovic, 2009). Thus a hearing handicap as a predictor of a negative effect of cochlear implantation on tinnitus is possibly mediated by a tinnitus handicap.

Our results should be read with caution due to the retrospective design, which might cause bias in two areas.

First, the retrospective method is susceptible to recall bias. Since participants completed the questionnaires after the implant surgery, it is possible that they could not remember the situation before implantation. This could magnify the effects; for example patients with a negative effect of implantation on tinnitus may remember the situation before implantation better than it actually was. This could result in lower preoperative tinnitus handicap scores and lower hearing handicap scores. This would mean that in our analyses of the negative effect of cochlear implantation on tinnitus, the predictive power of low preoperative tinnitus and hearing handicap is overestimated.

Second, there is potential contamination in the data because of factors such as social desirability and effort justification. Consequently, our data could be more in favour of a positive effect of cochlear implantation on tinnitus, because patients want to fulfil our

expectations (Schwartz & Sprangers, 2010). Social desirability and effort justification may affect the data in two ways: First, not all patients with a negative effect of cochlear implantation on tinnitus might mention their negative effect in our questionnaires, which could bias our study populations. Second, patients might score their preoperative tinnitus and hearing handicap higher and again falsely make these factors predictors for a negative effect of cochlear implantation on tinnitus.

CONCLUSION

A logistic analysis of possible predictive indicators of the effect of cochlear implantation on tinnitus did not reveal a good predictive model for a positive effect. In contrast, the negative effects of cochlear implantation on tinnitus could be modelled and were mainly related to low preoperative tinnitus and low hearing handicap scores. This predictive model needs to be viewed with caution due to the retrospective character of our study. More research needs to be done, preferable in a big prospective study, to make this model instrumental for clinical decision making and pre-operative patient counselling. However, our results might suggest that preoperative THQ and APHAB screening could be meaningful. Especially in patients who are afraid to develop tinnitus or tinnitus worsening as complication of cochlear implantation.

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REFERENCES

- Amoodi, H. A., Mick, P. T., Shipp, D. B., Friesen, L. M., Nedzelski, J. M., Chen, J. M., & Lin, V. Y. W. (2011). The effects of unilateral cochlear implantation on the tinnitus handicap inventory and the influence on quality of life. *Laryngoscope*. <https://doi.org/10.1002/lary.21851>
- Andersson, G., Freijd, A., Baguley, D. M., & Idrizbegovic, E. (2009). Tinnitus Distress, Anxiety, Depression, and Hearing Problems among Cochlear Implant Patients with Tinnitus. *Journal of the American Academy of Audiology*. <https://doi.org/10.3766/jaaa.20.5.5>
- Cox, R. M., & Alexander, G. C. (1995). The abbreviated profile of hearing aid benefit. *Ear and Hearing*. <https://doi.org/10.1097/00003446-199504000-00005>
- Denollet, J. (2005). DS14: Standard assessment of negative affectivity, social inhibition, and type D personality. *Psychosomatic Medicine*. <https://doi.org/10.1097/01.psy.0000149256.81953.49>
- Eggermont, J. J., & Roberts, L. E. (2004). The neuroscience of tinnitus. *Trends in Neurosciences*. <https://doi.org/10.1016/j.tins.2004.08.010>
- Klooststra, F. J. J., Arnold, R., Hofman, R., & Van Dijk, P. (2015). Changes in tinnitus after cochlear implantation and its relation with psychological functioning. *Audiology and Neurotology*. <https://doi.org/10.1159/000365959>
- Kompis, M., Pelizzone, M., Dillier, N., Allum, J., Demin, N., & Senn, P. (2012). Tinnitus before and 6 months after cochlear implantation. *Audiology and Neurotology*. <https://doi.org/10.1159/000335126>
- Kuk, F. K., Tyler, R. S., Russell, D., & Jordan, H. (1990). The psychometric properties of a tinnitus handicap questionnaire. *Ear and Hearing*. <https://doi.org/10.1097/00003446-199012000-00005>
- Newman, C. W., Jacobson, G. P., & Spitzer, J. B. (1996). Development of the tinnitus handicap inventory. *Archives of Otolaryngology - Head and Neck Surgery*. <https://doi.org/10.1001/archotol.1996.01890140029007>
- Olze, H., Szczepek, A. J., Haupt, H., Förster, U., Zirke, N., Gräbel, S., & Mazurek, B. (2011). Cochlear implantation has a positive influence on quality of life, tinnitus, and psychological comorbidity. *Laryngoscope*. <https://doi.org/10.1002/lary.22145>
- Olze, H., Szczepek, A. J., Haupt, H., Zirke, N., Graebel, S., & Mazurek, B. (2011). The impact of cochlear implantation on tinnitus, stress and quality of life in postlingually deafened patients. *Audiology and Neurotology*. <https://doi.org/10.1159/000323847>
- Pan, T., Tyler, R. S., Ji, H., Coelho, C., Gehringer, A. K., & Gogel, S. A. (2009). Changes in the tinnitus handicap questionnaire after cochlear implantation. *American Journal of Audiology*. [https://doi.org/10.1044/1059-0889\(2009/07-0042\)](https://doi.org/10.1044/1059-0889(2009/07-0042))
- Scheier, M. F., & Carver, C. S. (1985). Optimism, coping, and health: assessment and implications of generalized outcome expectancies. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association*. <https://doi.org/10.1037/0278-6133.4.3.219>

- Schwartz, C. E., & Sprangers, M. A. G. (2010). Guidelines for improving the stringency of response shift research using the thentest. *Quality of Life Research*. <https://doi.org/10.1007/s11136-010-9585-9>
- Souliere, C. R., Kileny, P. R., Zwolan, T. A., & Kemink, J. L. (1992). Tinnitus Suppression Following Cochlear Implantation: A Multifactorial Investigation. *Archives of Otolaryngology--Head and Neck Surgery*. <https://doi.org/10.1001/archotol.1992.01880120017004>
- Van De Heyning, P., Vermeire, K., Diebl, M., Nopp, P., Anderson, I., & De Ridder, D. (2008). Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation. *Annals of Otology, Rhinology and Laryngology*. <https://doi.org/10.1177/000348940811700903>
- Vanneste, S., To, W. T., & De Ridder, D. (2011). The psychometric properties of the Tinnitus Handicap Questionnaire in a Dutch-speaking population. *Clinical Otolaryngology*. <https://doi.org/10.1111/j.1749-4486.2010.02256.x>
- Zeman, F., Koller, M., Figueiredo, R., Aazevedo, A., Rates, M., Coelho, C., ... Landgrebe, M. (2011). Tinnitus handicap inventory for evaluating treatment effects: Which changes are clinically relevant? *Otolaryngology - Head and Neck Surgery*. <https://doi.org/10.1177/0194599811403882>
- Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*. <https://doi.org/10.1111/j.1600-0447.1983.tb09716.x>

A PROSPECTIVE STUDY OF THE EFFECT OF COCHLEAR IMPLANTATION ON TINNITUS

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ABSTRACT

Previous studies show diverse and sometimes even contrary results both concerning the effect of cochlear implantation on tinnitus as well as the factors that can influence this effect. The aim of this prospective questionnaire study was to determine the effects of cochlear implantation on tinnitus and explore which factors can influence the effect of cochlear implantation on tinnitus. Forty-four of the patients implanted in our hospital returned two questionnaire packages; one before the cochlear implantation and one six months after implantation. Before implantation, 66% of the patients experienced tinnitus. This study shows that cochlear implantation can help to reduce tinnitus and the tinnitus handicap in at least 28% of the patients with preoperative tinnitus. In 72% of the patients the tinnitus remained after implantation. None of the patients developed tinnitus after implantation. A shorter duration of tinnitus prior to implantation, a more fluctuating type of tinnitus, a higher tinnitus handicap prior to implantation and a round-window surgical approach might have a positive influence on the effect of cochlear implantation on tinnitus, but further research is necessary to confirm these findings.

INTRODUCTION

Tinnitus is a very common problem that has existed for centuries: the oldest-known written report dates back to the ancient Egyptians and Mesopotamians [Stephens, 1984]. The prevalence of tinnitus in the general population ranges from 5% to 43%, of whom 12-30% suffer from tinnitus that lasts for more than five minutes at a time [McCormack, 2016]. From the patients who visited self-help groups because of their tinnitus 30-42%, are willing to use devices if this would significantly reduce their tinnitus, 52-62% are willing use medication for tinnitus reduction, and 13-38% are even willing to undergo invasive procedures to obtain significant tinnitus reduction [Tyler, 2012]. Although that tinnitus is a phenomenon that already has existed for centuries, its exact cause is still not known. There are several hypotheses about the cause of tinnitus: Many hypotheses have in common that central neural mechanisms play a key role in its development. Most of these hypotheses state that tinnitus is caused by maladaptive plastic changes in the central auditory pathways as a reaction to peripheral hearing loss [Cacace, 2016].

Within the population of cochlear-implant candidates, the prevalence of tinnitus is between 66-86% [Quaranta, 2004; Kompis, 2012; Baguley and Atlas, 2007; Hazell, 1995; Andersson, 2009]. This high prevalence is consistent with the fact that people with hearing impairment are more likely to suffer from tinnitus [Han, 2009]. Cochlear implantation is associated with post-operative reduction of tinnitus loudness and awareness [Di Nardo, 2007; Ruckenstein, 2001]. Previous studies show a positive effect of cochlear implantation on both tinnitus prevalence and the handicap it causes in up to 93% of the patients [Klooststra, 2015; Ruckenstein, 2001; Pan, 2009]. Unfortunately, cochlear implantation can also have a negative effect on tinnitus. In some studies, participants experienced a deterioration of their tinnitus or even developed tinnitus [Klooststra, 2015; Kompis, 2012; van Zon, 2016]. According to previous studies, the number of participants that experienced deterioration of tinnitus after cochlear implantation is between 4-26% [Kompis, 2012].

As cochlear implantation can be of value in reducing both the prevalence of tinnitus and the tinnitus handicap in patients that suffer from severe hearing problems, the aim of this prospective questionnaire study was to determine the effects of cochlear implantation on tinnitus and explore which factors can influence the effect of cochlear implantation on tinnitus. Previous studies show very diverse results, both concerning the effect of cochlear implantation on tinnitus as well as concerning the factors that can influence this effect [Klooststra, 2015; Ruckenstein, 2001; Pan, 2009; Kompis, 2012; van Zon, 2016].

For our study, we used several validated questionnaires, that enabled us to have a broad view over the effect that cochlear implantation might have on the patients that suffer from tinnitus. We also used tinnitus handicap questionnaires to determine how the presence of tinnitus influences daily life in cochlear implant patients. We used a hearing-handicap questionnaire to establish whether if cochlear implantation, besides improving phoneme scores, also improves hearing abilities in daily life. Last, we included an anxiety and depression questionnaire to assess the influence of tinnitus and hearing loss on these feelings.

MATERIAL AND METHODS

Procedure and Inclusion

A total of 63 successive CI candidates from the patient database Cochlear Implant North Netherlands (CINN) were asked to participate in this questionnaire study on tinnitus. All patients were implanted in the University Medical Center Groningen (UMCG) between 2010 and 2013. All of them were 18 years or older at the time of the study and gave their written, informed consent. As concluded by the Medical Ethics Committee of the University Medical Center Groningen, this study is not subject to the Dutch Law Medical-Scientific Research with Humans (Wet Medisch-wetenschappelijk Onderzoek met Mensen, WMO). The study was conducted in accordance with the Declaration of Helsinki and applicable Dutch laws.

Surgical techniques

Two surgical techniques were used for the cochlear implantation; the round-window insertion technique and the cochleostomy technique. In the first technique, the electrode insertion is done through the round window aperture. In the second technique, the electrode insertion is also done through the round window aperture, but the round window is enlarged using a small drill. It is thought that this round-window insertion technique causes less damage to the cochlea. The most common reason that the surgeons used the cochleostomy technique instead of the round window insertion technique was dependent on the sort of electrode that was implanted. The CI422 electrode of cochlear can be placed using the round window insertion technique and the CI24RE electrode and the Advanced Bionics electrode can only be placed by using the cochleostomy technique. In fewer cases the reason for using the cochleostomy technique was the position of the facial nerve what made it impossible to reach the round window.

Measures

In this prospective study, we sent the participating patients two questionnaire booklets. The first booklet was sent when the participant agreed to undergo cochlear implantation. It was thus completed weeks to a couple of months prior to the implantation. This booklet consisted of questions about the pre-operative situation. The second booklet was completed six months after the patient was implanted and consisted of questions about the postoperative situation. Each booklet contained several questionnaires about tinnitus characteristics, depression/anxiety and hearing status. Also, the UMCG anamnestic tinnitus questionnaire was included, which contained several questions about the characteristics of the tinnitus and the influence of the CI on tinnitus perception. Further information about the audiological tests, date of implantation, surgery method and processor type was collected from the clinical files of the patients.

Questionnaires

- Abbreviated Profile of Hearing Aid Benefit (APHAB)

We used the translated and validated Dutch version of the APHAB. The APHAB questionnaire assesses hearing ability and discomfort [Cox and Alexander, 1995]. It contains 24 questions that are divided into 4 subscales: the Ease of Communication scale (EC scale), the Background Noise scale (BN scale), the Reverberation scale (RV scale), and the Aversiveness scale (AV scale). The EC scale describes the ability to understand people in various situations. The BN scale describes how background noise affects the ability to understand conversations. The RV scale describes the influence of reverberation/echo in rooms on the hearing ability. The AV scale describes discomfort caused by unpleasant sounds. All of these subscales contain 6 items and the patient is asked to rate all of the questions according to how often situations occur. The 7 different gradations are the following: always (99% of the time), almost always (87%), generally (75%), half-the-time (50%), occasionally (25%), seldom (12%) and never (1%).

- Hospital Anxiety and Depression Scale (HADS)

We used the translated and validated Dutch version of the HADS [Spinhoven 1997]. The HADS questionnaire was developed to improve the early detection of patients with any form of an anxiety or depression disorder [Zigmond and Snaith, 1983]. The questionnaire contains 14 items: 7 about anxiety and 7 about depression. Patients answer the questions on a scale from 0 to 3. Subscale scores can be calculated for anxiety and depression. A score below 7 is neither an anxiety nor a depression problem, between 8-10 the score suggests a potential anxiety or depression disorder and a score beyond 11 indicates definite cases.

- Tinnitus Handicap Inventory (THI)

We used the translated and validated Dutch version of the THI. The THI questionnaire consists of 25 questions about the influence of tinnitus on activities of daily life [Newman, 1996]. The questionnaire contains 11 questions about the functional effects on tinnitus, 9 questions about the emotional responses to tinnitus and 5 questions about catastrophic response to tinnitus. Patients have to indicate if such situations occur. Every 'yes' counts for 4 points, every 'sometimes' for 2 points and every 'never' for 0 points. The scores are summed to a total score between 0 and 100. A score below 16 has been suggested to imply a slight handicap, a score from 18-38 mild tinnitus, a score from 38-56 corresponds to severe tinnitus and a score higher than 78 means that this patient suffers from catastrophic tinnitus [McCombe, 1999].

- Tinnitus Handicap Questionnaire (THQ)

The THQ is used to measure the perception of the psychological and physical well being in tinnitus patients. In this study, we used a Dutch translation of the questionnaire [Vanneste, 2011]. This questionnaire contains 27 questions, divided into 3 main categories: 'social, emotional and behavioral tinnitus effects', 'tinnitus and hearing' and 'outlook on tinnitus'. Patients answered whether or not they agreed with the statements on a scale from 0 to 100. Total scores are calculated per category, following which the mean THQ score is calculated [Kuk, 1990].

- UMCG anamnestic tinnitus questionnaire

This is a non-validated questionnaire that concerns tinnitus characteristics such as pitch, loudness and lateralization [Klooststra, 2015].

Statistical analysis

Pre- and post-operative questionnaire scores were analyzed and compared to identify significant differences in tinnitus and related patient parameters before and after cochlear implantation. We used the Kolmogorov-Smirnov test and histograms to assess whether variables met the criteria for a normal distribution. If a variable was normally distributed, we used a paired t-test to identify significant differences between pre- and post-operative scores within a group of patients. If the data were not normally distributed, we used the Wilcoxon signed-rank test to determine whether there was a significant difference. To compare differences between the separated groups in a not normally distributed population, the Mann-Whitney U test was used. For all statistical analyses we used SPSS version 23.

RESULTS

Participants

Of the 63 patients we contacted, 50 subjects (79.4%) returned the first package of questionnaires (26 males and 24 females). Forty-seven of these participants received a cochlear implant in our hospital. Three patients were not implanted; one died while on the waiting list, one decided not to be implanted and one was implanted in another hospital. Forty-four of the implanted patients also returned the postoperative package of questionnaires (figure 1).

Figure 1. Inclusion flowchart

Reasons for exclusion were: non-responders, patient that didn't undergo cochlear implantation and patients that died.

Before cochlear implantation, 33 out of 50 participants (66.0%) reported tinnitus. Postoperatively, 21 out of the 44 participants (47.7%) reported tinnitus. Twenty-one (47.7%) of the 44 participants who returned both the preoperative and postoperative questionnaire booklet suffered from both pre- and postoperative tinnitus, eight participants (18.2%) of these only experienced tinnitus before the implantation and 15 participants (34.1%) never experienced tinnitus. None of the participants developed tinnitus after implantation.

Background variables

Table 1 shows all results from the 44 participants who returned both the preoperative and the postoperative questionnaire booklets.

Focusing on the group of patients with preoperative tinnitus, 72.4% suffered from both post- and preoperative tinnitus and 27.6% suffered only from preoperative tinnitus. The mean number of years participants experienced tinnitus before cochlear implantation was 24.7 (SD 22.3, range 1-67). The group with only preoperative tinnitus experienced the tinnitus during significantly fewer years prior to implantation (5.2 years (SD=5.2, range 1-14)) compared to the group with both pre- and postoperative tinnitus (32.2 years (SD=21.9, range 1-67)) ($p<0.05$). Participants with preoperative tinnitus experienced tinnitus was 76.1% of the time (SD=30.1). This percentage was significantly higher in the group with both pre- and postoperative tinnitus (80.3%, SD=26.7) compared to the group with only preoperative tinnitus (65.9%, SD=31.2) ($p<0.05$). Patients with preoperative tinnitus experienced their tinnitus on average on 28 days per month (range 3-30).

Most patients experienced their tinnitus in both ears or somewhere central in the head. Only a few patients experience their tinnitus unilaterally. This was the case both for the preoperative situation as well as for the postoperative situation (table 1).

In both the preoperative and the postoperative situation, the tinnitus sounds perceived were diverse. Postoperatively no patient continued to perceive a tonal tinnitus sound.

Preoperatively almost half of the patients who answered this question experienced difficulties getting to sleep because of their tinnitus. Postoperatively fewer patients experienced this difficulty because of their tinnitus (table 1).

Tinnitus handicap

Within the participants with preoperative tinnitus, the mean preoperative THI score was 23 (SD=21.2), and the mean THQ score was 30.7 (SD=11.0). The group of participants with only preoperative tinnitus had higher preoperative scores on both the THI (31.8/20.5, $p=0.77$) and THQ (31.8/30.3, $p=0.19$) compared to the THI and THQ scores of participants with both pre- and postoperative tinnitus. However, this difference is not significant.

Table 1: patient characteristics and changes after CI implant.				
	Patients without tinnitus	All patients with preoperative tinnitus	Only preoperative tinnitus	Both pre- and postoperative tinnitus
Number of patients	15	29	8	21
Percentage	-	100	27.6	72.4
Gender (male/female), n	8/7 (n=15)	14/15 (n=29)	2/6 (n=8)	12/9 (n=21)
Age (at implantation)	62.8 (SD 14.8, n=15)	64.2 (SD 14.9, n=29)	60.0 (SD 20.1, n=8)	66.0 (SD 12.6, n=21)
CI ear (right/left), n	10/5 (n=15)	14/15 (n=29)	5/3 (n=8)	9/12 (n=21)
Brand (Cochlear/Advanced Bionics), n	14/1 (n=15)	26/3 (n=29)	7/1 (n=8)	19/2 (n=21)
Operation method (cochleostomy/round window), n	7/8 (n=15)	15/13 (n=28)	2/6 (n=8)	13/7 (n=20)
Years of preoperative tinnitus	-	24.7 (SD 22.3, n=18)	5.2 (SD 5.2, n=5)	32.2 (SD 21.9, n=13)
Percent of the time tinnitus pre/postop	-	76.1 (SD 30.1, n=28)	65.9 (SD 31.2, n=8)	80.3 (SD 26.7, n=20)
Number of days tinnitus per month pre/postop	-	28.0 (SD 6.6, n=28)	26.6 (SD 9.5, n=8)	27.9 (SD 6.3, n=16)
TH pre/postop	-	23.6 (SD 21.2, n=29)	31.8 (SD 26.2, n=8)	20.5 (SD 18.9, n=21)
THQ pre/postop	-	30.7 (SD 11.0, n=23)	31.8 (SD 13.0, n=5)	30.3 (SD 10.8, n=18)
Side of tinnitus preoperative number left/right/both	-	2 / 1 / 31	-	-
Side of tinnitus postoperative CI on number left/right/both	-	-	-	1 / 3 / 13
Side of tinnitus postoperative CI off number left/right/both	-	-	-	2 / 3 / 15
Sound of tinnitus preoperative number diverse/whistletonal	-	26 / 4 / 1	-	-
Sound of tinnitus postoperative CI on number diverse/whistletonal	-	-	-	14 / 2 / 0
Sound of tinnitus postoperative CI off number diverse/whistletonal	-	-	-	17 / 3 / 0
Tinnitus influence on sleep preoperative number yes/sometimes/no	-	5 / 15 / 13	-	-
Tinnitus influence on sleep postoperative number yes/sometimes/no	-	-	-	1 / 7 / 13
Loudness preoperative	-	46.6 (SD 22.8, n=26)	43.1 (SD 28.2, n=8)	60.5 (SD 20.1, n=20)
Loudness postoperative, CI on (compared to preoperative situation)	-	-	-	43.6 (SD 35.7, n=18)*
Loudness postoperative, CI off (compared to preoperative situation)	-	-	-	50.8 (SD 32.2, n=18)
Pitch preoperative	-	55.5 (SD 23.5, n=28)	47.9 (SD 20.6, n=7)	46.2 (SD 24.0, n=19)
Pitch postoperative, CI on (compared to preoperative situation)	-	-	-	45.9 (SD 34.0, n=16)
Pitch postoperative, CI off (compared to preoperative situation)	-	-	-	55.0 (SD 30.4, n=16)
Phonemescore pre/postop	36.1 (SD 15.6, n=14)	67.3 (SD 23.7, n=15)**	37.5 (SD 16.7, n=8)	40.5 (SD 18.1, n=19)
APHAB pre/postop	77.2 (SD 12, n=15)	44.9 (SD 18.7, n=9)**	77.2 (SD 12.0, n=8)	79.8 (SD 16.2, n=19)
Preoperative hearing aids (yes/no), n	13/2 (n=15)	23/6 (n=29)	7/1 (n=8)	16/5 (n=21)
Mean anxiety score, pre/postop	3.1 (SD 3.8, n=14)	1.1 (SD 1.3, n=14)*	6.9 (SD 4.8, n=8)	4.7 (SD 2.9, n=20)
Mean depression score, pre/postop	2.8 (SD 3.2, n=14)	2.9 (SD 3.5, n=13)	4.3 (SD 3.1, n=8)	4.5 (SD 2.6, n=20)

* Preoperative and postoperative scores are significantly different at P<0.05; ** preoperative and postoperative scores are significantly different at P<0.01

Figure 2 visualises the changes in tinnitus handicap in the group of participants with both pre- and postoperative tinnitus. This scatterplot shows the THI and THQ scores of all individuals in both the pre- and postoperative situation. All dots above the line show deterioration in the tinnitus handicap, the dots below the line show improvement compared to the preoperative situation. Most of the dots (THI 12 out of 17, THQ 9 out of 14) are beneath the diagonal, which implies a majority of the participants showed improvement in their THI and/or THQ scores after cochlear implantation. Previous studies mention contrary results concerning the minimum change of the Tinnitus Handicap Inventory (THI) score that could be considered clinically relevant. Seven of the patients had a significant reduction of 7 points or more on the THI [Zeman, 2011] and only one patient had a significant reduction of 20 points or more on the THI [Newman, 1998].

Figure 2. Scattered plot of tinnitus handicap score

This scattered plot shows the pre- and postoperative THI and THQ scores from every participant that completed the corresponding questionnaire. Dots that are beneath the line show a improvement in tinnitus handicap, dots above the line show a deterioration in tinnitus handicap. There are 16 THI dots instead of 17, because two participants scored the exact same pre- and postoperative score (preoperative 6 and postoperative 8).

According to Spearman's correlation test there was no significant correlation between the postoperative scores on the THI and THQ and the postoperative phoneme scores, respectively -0.044 , $p=0.859$ for the THI and 0.209 , $p=0.404$ for the THQ. Also, there was no significant correlation between the postoperative scores on the THI and the postoperative scores on the APHAB, 0.336 , $p=0.148$. However there was a significant correlation between the postoperative scores on the THQ and the postoperative scores on the APHAB, 0.529 , $p<0.05$.

Loudness and pitch

In the anamnestic tinnitus questionnaire, tinnitus loudness and pitch were measured on a visual analogue scale with a range from 0-100. The preoperative tinnitus loudness scored somewhat higher within the group that suffered from both pre- and postoperative tinnitus (60.5 , $SD=20.1$) compared to the group with only preoperative tinnitus (43.1 , $SD=28.2$). However, this difference was not significant ($p=0.10$). Within the group of participants with both pre- and postoperative tinnitus the mean tinnitus loudness was significantly lower in the postoperative situation when the CI was turned on compared to the preoperative situation. This difference was not found when the CI was turned off.

Comparing the group with only preoperative tinnitus with the group with both pre- and postoperative tinnitus, no significant difference in preoperative pitch score was found ($p=0.91$). The mean tinnitus pitch of participants with both pre- and postoperative tinnitus changed from 46.2 ($SD\ 24.0$) in the preoperative situation to 45.9 ($SD\ 34.0$) in the postoperative situation when the CI was turned on. When the CI was turned off, this postoperative pitch was somewhat higher (55.0 ($SD\ 30.4$)). However, these differences were not significant.

Surgical details

Twenty-four of the patients were implanted in their right ear and 20 in their left ear. Most of the participants received a device of the manufacturer Cochlear ($n=40$), the remaining participants received an Advanced Bionics implant ($n=4$). As noted in the methods two surgical implantation techniques were used; the cochleostomy technique (22 patients) and the round window insertion technique (21 patients). In one patient, the technique used had not been recorded.. Using the Mann-Whitney U test revealed no significant difference between surgical techniques between the group with and without postoperative tinnitus ($p=0.06$), but in the group where the tinnitus remained, 65% of the patients were operated using the cochleostomy technique, whereas in the group where the tinnitus ceased only 25% of the patients were operated using this technique.

Hearing ability

All groups of patients showed a significant improvement in the phoneme scores after cochlear implantation, which indicated that their hearing ability had improved. Also, the hearing handicap, as measured by the APHAB, was significantly lower in all groups. -

Anxiety and depression*Anxiety*

Both in the group with (5.3/3.8, $p<0.05$) and without (3.1/1.1, $p<0.05$) preoperative tinnitus the mean anxiety scores were significantly lower postoperatively compared to preoperatively. The postoperative anxiety score (3.9; SD=3.9) was also significantly lower than the preoperative score (6.9; SD=4.8) in the group of patients with only preoperative tinnitus. This difference was not significant in the group with both pre- and postoperative tinnitus, being 4.7 (SD=2.9) preoperatively and 3.7 (SD=3.4) postoperatively.

A clinical HADS score of >8 was present in two patients in the preoperative situation. Both these patients suffered only from preoperative- and not postoperative tinnitus. One of these patients still had a score of >8 in the postoperative situation. None of the other patients scored higher than 8 after cochlear implantation.

Depression

Both in the group with (4.4/3.2) and without (2.8/2.9) preoperative tinnitus there was no significant difference in the mean depression score preoperatively compared to postoperatively. Neither were significant differences found in the groups with both pre- and postoperative tinnitus or with only preoperative tinnitus. One patient scored >8 on the HADS preoperative and had suffered from both pre- and postoperative tinnitus. There were 2 patients that scored >8 on the HADS after implantation: One of them only suffered from preoperative tinnitus and the other suffered from both pre- and postoperative tinnitus. Neither of these patients was the one person with a high preoperative depression score.

DISCUSSION

In this prospective study, we investigated the influence of cochlear implantation on tinnitus in patients who received a cochlear implant because of their severe hearing loss. Our study showed that in 27.6% of the patients with preoperative tinnitus, the tinnitus disappeared after cochlear implantation. In the group of patients where the tinnitus remained after

cochlear implantation, most of the patients showed lower tinnitus handicap scores and lower tinnitus loudness scores after the operation. The patients in the group where the tinnitus disappeared showed fewer years of tinnitus prior to implantation, experienced their tinnitus for less time during the day prior to implantation, experienced more tinnitus handicap prior to implantation and were more often operated on using the round-window approach compared to the patients whose the tinnitus had remained.

Our result that tinnitus cessation occurs in 27.6% (n=8) of the patients with preoperative tinnitus is in line with the numbers described in previous studies, which report suppression of tinnitus after cochlear implantation in 15-95% of the patients [Kompis, 2012; Quaranta, 2008; Van de Heyning, 2008; Akdogan, 2009; Bovo, 2010; Pan, 2009; Rubinstein, 2003]. Our percentage is somewhat low in this range, probably because our number only describes the patients with tinnitus cessation and does not include the patients who experienced improvement of their tinnitus. Figure 2 shows that also about 2/3 of the 21 patients with persistent tinnitus after cochlear implantation have lower tinnitus handicap scores after cochlear implantation, so we estimate that the percentage of patients with at least partial tinnitus suppression after cochlear implantation is close to 75% (n=8+14=21/29).

In the group of participants where tinnitus did not disappear in the postoperative situation, the mean time they experienced tinnitus prior to implantation was 32.2 years (SD=21.9, range 1-67). Within participants without postoperative tinnitus this was only 5.2 years (SD=5.2, range 1-14). The duration of suffering from tinnitus prior to implantation may influence the chance of the tinnitus disappearing with cochlear implantation. This finding can be explained by the theory that tinnitus results from an increase in spontaneous neural activity and plastic re-organization of the central nervous system. It is possible that these neural changes are harder to undo when they have existed for a longer time before treatment was started, because of less plasticity. There are no previous studies that report duration of tinnitus prior to implantation influences the effect of cochlear implantation on tinnitus. However, there are previous studies that report that the number of years of hearing loss prior to implantation can have this influence [Olze et al., 2011a, Olze et al., 2011b]

Our study also shows that patients with tinnitus cessation after cochlear implantation experience their tinnitus for less time per day compared to the patients in whom the tinnitus remained after implantation. This could mean that the patients with tinnitus cessation after cochlear implantation suffer more from fluctuating tinnitus, while the patients in whom the tinnitus remained suffer more from a continuous tinnitus. Possibly,

a more fluctuating tinnitus is more easily treated than a more continuous tinnitus, because the changes in the central nervous system could be less prominent in patient with a fluctuating tinnitus. However, no other studies confirm these results.

The participants who experienced tinnitus cessation also experienced a higher preoperative tinnitus handicap (both THI and THQ) than the participants that still retained their tinnitus in the postoperative situation. This suggests that the more inconvenience experienced from tinnitus before cochlear implantation, the more likely it is that tinnitus will cease after implantation. This finding was also described in previous studies [Kim, 2013; Ramakers, 2015].

The surgical approach is another possible predictive factor for the effect of cochlear implantation on tinnitus. Within the group without postoperative tinnitus, most of the participants (75.0%) were operated using a round-window insertion. Within the group that still experienced tinnitus postoperatively, this was only 35.0%. This finding suggests that using a round-window insertion increases the chance that the tinnitus will disappear after the cochlear implantation, compared to using a separate cochleostomy. An explanation for this finding is that surgery using a round window insertion with a slimmer electrode may cause less damage to the cochlea and hair cells. Thus, this technique offers a higher chance of preserving the residual hearing of the patients and diminishes the chance of further reducing the afferent input to the brain, and thereby maintaining or worsening the tinnitus.

CONCLUSION

Tinnitus is a very common problem of CI candidates and CI users. This study shows that cochlear implantation can help to reduce tinnitus and tinnitus handicap. A shorter duration of tinnitus prior to implantation, a tonal tinnitus, a higher tinnitus handicap prior to implantation and a round window insertion operation technique correlate with a positive influence of cochlear implantation on tinnitus. Further research is necessary in a larger and a more uniform study population with regard to hearing abilities, age and type of tinnitus (unilateral/tonal) .

REFERENCES

- Akdogan O, Ozcan I, Ozbek C, Dere H: Tinnitus after cochlear implantation. *Auris Nasus Larynx* 2009;36:210-212.
- Andersson G, Freijd A, Baguley DM, Idrizbegovic E: Tinnitus distress, anxiety, depression, and hearing problems among cochlear implant patients with tinnitus. *J Am Acad Audiol* 2009;20:315-319.
- Baguley DM, Atlas MD: Cochlear implants and tinnitus. *Prog Brain Res* 2007;166:347-355.
- Bovo R, Ciorba A, Martini A: Tinnitus and cochlear implants. *Auris Nasus Larynx* 2011;38:14-20.
- Cacace AT, de Kleine E, Holt AG, van Dijk P: Scientific foundations of audiology, perspectives from physics, biology, modeling and medicine. Plural Publishing 2016; Chapter 15, 351-369.
- Cox RM, Alexander GC: The abbreviated profile of hearing aid benefit. *Ear Hear* 1995;16:176-186.
- Di Nardo W, Cantore I, Cianfrone F, Melillo P, Scorpecci A, Paludetti G: Tinnitus modifications after cochlear implantation. *Eur Arch Otorhinolaryngol* 2007;264:1145-1149.
- Han BI, Lee HW, Kim TY, Lim JS, Shin KS: Tinnitus: characteristics, causes, mechanisms and treatments. *J Clin Neurol* 2009;5:11-19.
- Hazell JW, McKinney CJ, Aleksy W: Mechanisms of tinnitus in profound deafness. *Ann Otol Rhinol Laryngol Suppl* 1995;166:418-420.
- Van de Heyning P, Vermeire K, Diebl M, Nopp P, Anderson I, De Ridder D: Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation. *Ann Otol Rhinol Laryngol* 2008;117:645-652.
- Kim DK, Bae SC, Park KH, Jun BC, Lee DH, Yeo SW, Park SN: Tinnitus in patients with profound hearing loss and the effect of cochlear implantation. *Eur Arch Otorhinolaryngol* 2013;270:1803-1808.
- Kloofstra FJ, Arnold R, Hofman R, van Dijk P: Changes in tinnitus after cochlear implantation and its relation with psychological functioning. *Audiol Neurotol* 2015;20:81-89.
- Kompis M, Pelizzone M, Dillier N, Allum J, DeMin N, Senn P: Tinnitus before and 6 months after cochlear implantation. *Audiol Neurotol* 2012;17:161-168.
- Kuk FK, Tyler RS, Russell D, Jordan H: The psychometric properties of a tinnitus handicap questionnaire. *Ear Hear* 1990;11:434-445.
- McCombe A, Baguley D, Coles R, McKenna L, McKinney C, Windle-Taylor P: Guidelines for grading of tinnitus severity: the results of a working group commissioned by the British association of Otolaryngologists, Head and Neck Surgeons, 1999. *Clin Otolaryngol Allied Sci* 2001;26:388-393.
- McCormack A, Edmonson-Jones M, Somerset S, Hall B: A systematic review of the reporting of tinnitus prevalence and severity. *Hearing res* 2016;337:70-79.
- Newman CW, Jacobsen GP, Spitzer JB: Development of the Tinnitus Handicap Inventory. *Arch Otolaryngol Head Neck Surg* 1996;122:143-148.

- Newman CW, Sandridge SA, Jacobson GP: Psychometric adequacy of the Tinnitus Handicap Inventory (THI) for evaluating treatment outcome. *J Am Acad Audiol* 1998;9:153-160.
- Olze H, Szczepek AJ, Haupt H, Forster U, Zirke N, Grabel S, Mazurek B: Cochlear implantation has a positive influence on quality of life, tinnitus and psychological comorbidity. *Laryngoscope* 2011;121:2220-2227.
- Olze H, Szczepek AJ, Haupt H, Zirke N, Graebel S, Mazurek B: The impact of cochlear implantation on tinnitus, stress and quality of life in postlingually deafened patients. *Audiol Neurotol* 2012;17:2-11.
- Pan T, Tyler RS, Ji H, Coelho C, Gehringer AK, Gogel SA: Changes in the tinnitus handicap questionnaire after cochlear implantation. *Am J Audiol* 2009;18:144-51.
- Quaranta N, Fernandez-Vega S, D'Elia C, Filipo R, Quaranta A: The effect of unilateral multichannel cochlear implant on bilaterally perceived tinnitus. *Acta Otolaryngol* 2008;128:159-163.
- Quaranta N, Wagstaff S, Baguley DM: Tinnitus and cochlear implantation. *Int J Audiol* 2004;43:245-251.
- Ramakers GG, van Zon A, Stegeman I, Grolman W: The effect of cochlear implantation on tinnitus in patients with bilateral hearing loss: a systematic review. *Laryngoscope* 2015;125:2584-2592.
- Rubinstein JT, Tyler RS, Johnson A, Brown CJ: Electrical suppression of tinnitus with high-rate pulse trains. *Otol Neurotol* 2003;24:478-485.
- Ruckenstein MJ, Hedgepeth C, Rafter KO, Montes ML, Bigelow DC: Tinnitus suppression in patients with cochlear implants. *Otol Neurotol* 2001;22:200-204.
- Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, van Hemert AM: A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med* 1997;27:363-370.
- Stephens SD: The treatment of tinnitus-a historical perspective. *J Laryngol Otol* 1984;98:963-972.
- Tyler R: Patient preferences and willingness to pay for tinnitus treatments. *J Am Acad Audiol* 2012;23:115-125.
- Vanneste S, To WT, de Ridder D: The psychometric properties of the tinnitus handicap questionnaire in a Dutch speaking population. *Clin Otolaryngol* 2011;36:9-16.
- Zigmond AS, Snaith RP: The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361-370.
- Zeman F, Koller M, Figueiredo RR, Azevedo AA, Rates M, Coelho C, Kleinjung T, de Ridder D, Langguth B, Landgrebe M: Tinnitus Handicap Inventory for Evaluating Treatment Effects: Which Changes Are Clinically Relevant?. *Otolaryngology Head and Neck Surgery*, 2011; 145(2):282-7.
- van Zon A, Smulders YE, Ramakers GG, Stegeman I, Smit AL, Van Zanten GA, Stokroos RJ, Hendrice N, Free RH, Maat B, Frijns JH, Mylanus EA, Huinck WJ, Topsakal V, Tange RA, Grolman W: Effect of unilateral and simultaneous bilateral cochlear implantation on tinnitus: a prospective study. *Laryngoscope* 2016;126:956-961.

CHANGES IN TINNITUS BY COCHLEAR IMPLANTATION: A PARAMETRIC STUDY OF THE EFFECT OF SINGLE-ELECTRODE STIMULATION

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ABSTRACT

Introduction

While cochlear implantation may have a positive effect on tinnitus, it is not effective in reducing tinnitus in all patients. This may be due to different patients requiring different strategies of electrical stimulation in order to obtain a positive effect on tinnitus. It is, therefore, important to identify the most effective stimulation strategies to reduce tinnitus. The simplest possible strategy is stimulation by only one electrode. In this study, we investigated tinnitus suppression by electrical stimulation via a single-electrode of the cochlear implant.

Methods

We performed a listening experiment in 19 adult participants, who had received a unilateral cochlear implant (CI) because of severe bilateral hearing loss. All of these patients had indicated that they suffered from tinnitus. During a 300-second interval, patients listened to blocks of single-electrode stimulation and rated the loudness of the stimulus and any effects on their tinnitus. The 300-second interval included a block of single-electrode stimulation (duration 120 seconds). In consecutive intervals, the stimulus differed in its cochlear location (basal or apical), its pulse rate (720 or /725Hz, 1200Hz, 2400 or /2320Hz), and amplitude (just above threshold or equivalent to moderate loudness). Thus, $2 \times 3 \times 2 = 12$ stimulus conditions were tested in each participant and each condition was presented only once. During the experiment, the participants promptly rated the loudness of the stimuli and the loudness of their tinnitus on a Visual Analogue Scale (10-point VAS).

Results

Significantly more tinnitus reduction was observed with stimuli at a moderate intensity level (30%) compared to stimuli at near-threshold level (18%) ($\text{Chi}^2 \text{ } p < 0.01$). No significant differences in tinnitus levels resulted from the different pulse rates and stimulation sites. Eight participants reported an increase of tinnitus loudness under at least one stimulus condition. Changes in tinnitus loudness were generally minor, and never exceeded 3 points on the VAS scale. The overall effect of cochlear implantation on tinnitus, i.e. the effect with full-array stimulation, was not correlated with the effectiveness of the single-electrode stimulation on tinnitus.

Conclusion

In conclusion, the effect of single-electrode stimulation on tinnitus is relatively insignificant in comparison to the effect of full-array stimulation. However, in some individual cases, sustained single electrode stimulation may be beneficial for tinnitus management.

INTRODUCTION

A wide variety of approaches has been explored to suppress tinnitus by electrical stimulation. Stimulation has been applied via electrodes placed at various anatomical locations in the central or in the peripheral auditory system. Stimulation sites included the mastoid bone, the tympanic membrane, the promontory, the round window, and via a cochlear implant in the scala tympani [Kleine Punte et al., 2013; Zeng et al., 2011; Konopka et al., 2001; Graham, and Hazellf, 1977; Okusa et al., 1993; Portmann et al., 1979; Dobie et al., 1986; Shulman, 1987; Watanabe et al., 1997; Arts et al., 2015b; Rubinstein et al., 2003; Jastreboff, and azell, 1993; Arts et al., 2015a; Aran, and Cazals, 2008; Arts et al., 2016; Mertens et al., 2018]. The stimulation strategies also vary substantially, using direct current (DC), or alternating current (AC). Evidence suggests that the closer the active electrode is situated to the neural and sensory elements of the cochlea, the better the results are [Portmann et al., 1979; Dobie et al., 1986; Aran, and Cazals, 2008]. Direct current stimulation causes more often more complete tinnitus suppression than alternating current stimulation [Portmann et al., 1979; Aran, and Cazals, 2008].

Among the various approaches using electrical stimulation to suppress tinnitus, cochlear implantation is the most successful so far [Kleine Punte et al., 2013; Zeng et al., 2011; Quaranta et al., 2008; Van De Heyning et al., 2008; Akdogan et al., 2009; Bovo et al., 2011; Pan et al., 2009; Arts et al., 2015a; Arts et al., 2015b; Arts et al., 2016; Mertens et al., 2018] Kleine Punte et. al. (2013) demonstrated that full-length stimulation is the most effective manner to reduce tinnitus in cochlear implant patients. However, not all such patients benefit from full-length stimulation and it remains necessary to search for other stimulation strategies to suppress tinnitus using a CI [Mo et al., 2002; Kompis et al., 2012; Arts et al., 2012; Akdogan et al., 2009; Bovo et al., 2011; Pan et al., 2009; Tyler, 1994; Di Nardo et al., 2007; Arts et al., 2015b; Arts et al., 2015a]. In the study of Kleine Punte et. al. (2013) only stimuli at the basal electrodes were tested regarding a reduction of tinnitus by (single) electrode stimulation. Other previous studies also only partially explored single-electrode stimulation. In this study, we broadened the parameter space by using a large number of possible stimulation configurations via a cochlear implant, both in terms of the cochlear electrode location, stimulation rate and amplitude. We aimed to systematically explore the various parameters of single-electrode stimulation and investigate their effect in a relatively large group of participants. If these single electrode stimuli are effective in tinnitus reduction, they could potentially be added to full-electrode stimulation for speech comprehension in patients who do not experience tinnitus reduction by full-electrode stimulation alone.

We describe a parametric study of tinnitus suppression, using electrical stimulation by means of a CI, where just one electrode of the cochlear implant array was activated. The purposes of this study were to investigate (1) whether single-electrode stimulation can reduce tinnitus loudness and (2) whether tinnitus suppression with single-electrode stimulation depends on the electrode location, stimulation pulse rate, or stimulation amplitude.

MATERIALS AND METHODS

Subjects

For this study, all CI patients who were implanted at the University Medical Center Groningen in the period from 2000 until 2009 received a letter asking for their participation. All were 18 years of age or older and were implanted at least 6 months before the current set of experiments. Among those who positively reacted to our letter, there were 19 CI patients who as adults received a unilateral cochlear implant because of bilateral severe hearing loss (standard of care in the Netherlands) and had suffered from subjective, chronic and constant tinnitus in daily life for more than three months. The current study was not aimed at reducing the tinnitus handicap. Rather, we were interested in reducing the tinnitus percept irrespective of the handicap the tinnitus possibly posed. Hence, both subjects with low and high handicap scores (THI or THQ) and with all kinds of effects of full-length stimulation through the CI on their tinnitus (tinnitus onset, no effect on tinnitus, tinnitus reduction), qualified for participation. Patients were implanted with CI from the companies Cochlear Inc. (implant types CI24R CA, CI24R CS, CI24RE CA) or Advanced Bionics Inc. (Hi Res 90K Helix). The study was approved by the Medical Ethical Committee of the University Medical Center Groningen and informed consent obtained from all subjects.

Study design

A listening experiment was performed, during which patients were presented with an electrical pulse train via a single CI electrode. The stimuli were generated by clinical software and presented via the clinical sound processor of the patient while connected to the standard clinical interface.

The software allowed for the presentation of blocks of 5 seconds of single-electrode stimulation; 24 blocks combined to 120 seconds. Subjects indicated the loudness of the stimulus and the loudness of their tinnitus on a Visual Analogue Scale (0-10, with 0 being

inaudible and 10 being very loud). Subjects were instructed to indicate the loudness every 15 seconds, and to rate their tinnitus regardless of its laterality. Loudness rating started 60 seconds prior to the stimulus presentation. Next, a single electrode was activated for 120 seconds, and finally there were 120 seconds without stimulus. Thus, loudness estimates were acquired for a total of $60+120+120=300$ seconds.

A total of 12 stimulus conditions were tested, during which (1) the position of stimulation in the cochlea, (2) the stimulation rate, and (3) the stimulation amplitude were varied. The electrode position was either a basal or an apical electrode. For devices of the Cochlear company, the electrode array consisted of 22 electrodes. The activated basal and apical electrodes, respectively, were chosen to be #3 and #20. For Advanced Bionics devices, the electrode array contained 16 electrode contacts, which are labeled from apex to base. The basal and apical electrodes used for stimulation, were #14 and #3 respectively. The pulse rates were 720 (low), 1200 (medium), and 2400 (high) Hz for Cochlear, and 725 (low), 1200 (medium) and 2320 (high) Hz for Advanced Bionics. The amplitude of the stimulation pulses was set to correspond to a level that was either just audible, or was clearly perceived and judged to be of moderate loudness by the participant. These levels were termed T (for threshold) or C (for comfortable), respectively, and established for each patient just prior to the experiment. In the subsequent text we refer to the near-threshold level as the T level and about the moderate-intensity level as the C level.

With 2 different locations of stimulation, 3 different pulse rates and 2 different amplitude levels, the total number of stimulus conditions was 12. Thus, with 300 seconds per stimulus, the full experiment lasted 60 minutes, excluding frequent breaks. The order in which the stimuli were presented to the patients was randomized. Two patients did not complete the entire experiment, due to tiredness and concentration problems. Of these patients one received 10 stimuli (patient 1) and the second 8 stimuli (patient 2).

Descriptive variables

Besides using the VAS as the primary outcome measure, we collected data on the lateralization of tinnitus, the anamnestic effect of the cochlear implant on tinnitus in daily life (full-array stimulation), and the postoperative tinnitus handicap scores by means of questionnaires (Tinnitus Handicap Inventory (THI); Tinnitus Handicap Questionnaire (THQ)) which were completed just prior to the experiment.

Statistical analysis

To describe the effect on tinnitus loudness, we counted the number of stimulus conditions for which the tinnitus either decreased, remained unchanged, or increased. Tinnitus was scored 'decreased' when the mean score on the VAS of the tinnitus during stimulation was reduced by at least one point compared to the mean score on the VAS prior to the stimulus. An 'increase' of tinnitus was scored when the mean score on the VAS during stimulation increased at least one point compared to the mean score on the VAS prior to stimulation. No effect was scored when the mean score on the VAS remained stable, or was reduced/increased less than one point during stimulation. Chi Square tests were used to assess whether there was a significant influence of electrode position, pulse rate, or level of stimulation on the decrease of tinnitus during stimulation. Statistical significance was defined as $p < 0.05$, using SPSS 20.0 to perform the analyses.

A non-parametric Mann-Whitney U test was used to assess whether there was a significant difference between the tinnitus handicap scores of the patients who experienced tinnitus suppression and the patients who did not.

RESULTS

We included seven females and 12 males; the age of the patients ranged from 43 to 78 years at the time of the experiments.

Figure 1 shows an example of the raw traces of the VAS for both the stimulus and tinnitus of a patient with a stimulus from the apical electrode, with a medium pulse rate and a moderate intensity level. The stimulus rating was zero on the VAS at the beginning of the experiment, increased to 3 during the stimulus and returned to zero after the stimulus offset. Simultaneously, the VAS of the tinnitus started at three, decreased to two during the stimulus and remained at two, until 45 seconds after the stimulus offset. Eventually, the tinnitus returned to its original loudness.

The stimulus VAS trace in figure 1 is representative for the stimulus VAS traces of all patients obtained during this experiment. The stimuli at low intensity level (T-level) (mean VAS 1.1, SD 0.2) were rated lower compared to the stimuli at moderate intensity level (C-level) (mean VAS 5.0, SD 0.5). The traces of the VAS of the tinnitus varied greatly across patients and stimulus conditions. In 9 patients, tinnitus returned to its pre-stimulus level immediately after the stimulus ended. In 8 patients, in 50% of the

Figure 1. The raw traces of the VAS for both the stimulus and tinnitus of patient number five using a stimulus at the apical electrode, with a pulse rate of 1200 Hz and the stimulus at C-level. The arrows mark the duration of the stimulus.

conditions that caused a reduction of the tinnitus, the tinnitus remained suppressed up to 240 seconds (end of trial).

Table 1 shows patient characteristics, causes of hearing loss, the scores of the tinnitus handicap questionnaires, implant type, the overall anamnestic effect of cochlear implantation on tinnitus and the effect of stimuli for each subject.

Table 1: patient characteristics and in the rightmost three columns the effect of single electrode stimulation

Patient number	Male/Female	Age (yrs)	Etiology of hearing loss	THI	THQ	Implant type	Overall anamnestic effect of CI on tinnitus	Tinnitus reduction*	No effect*	Tinnitus increase*
1	Female	62	unknown	12	26	Cochlear	No effect	4	5	1
2	Male	74	otosclerosis	33	20	Cochlear	No effect	0	8	0
3	Male	78	unknown	46	85	Cochlear	Reduction	0	12	0
4	Male	53	congenital	60	68	Cochlear	Reduction	3	9	0
5	Male	69	unknown	30	53	Advanced Bionics	Reduction	10	2	0
6	Male	59	unknown	22	14	Cochlear	Reduction	1	10	1
7	Male	70	unknown	0	6	Advanced Bionics	No effect	0	12	0
8	Female	46	M. Meniere	46	76	Cochlear	Reduction	8	4	0
9	Female	65	otosclerosis	0	22	Cochlear	Increase	1	2	9
10	Male	64	familial	36	41	Cochlear	Increase	0	12	0
11	Female	69	familial	40	61	Advanced Bionics	Increase	9	0	3
12	Male	47	meningitis	0	0	Cochlear	Reduction	2	7	3
13	Female	45	unknown	22	26	Cochlear	Increase	0	10	2
14	Male	43	otosclerosis	42	57	Cochlear	No effect	1	11	0
15	Male	68	sculbasefracture	12	37	Advanced Bionics	No effect	6	6	0
16	Female	59	otitis	68	59	Cochlear	No effect	3	9	0
17	Male	57	ISSHL	4	11	Cochlear	No effect	0	12	0
18	Female	69	unknown	0	0	Cochlear	No effect	4	2	6
19	Male	55	unknown	66	71	Cochlear	Onset	2	3	7
Mean		60.6		28.4	38.6		No effect	2.8	7.2	1.7
Range		43-78		0-68	0-85			0-10	0-12	0-9

Patients 1 and 2 did not complete the entire experiment, *number of conditions with the indicated effect of single electrode stimulation

THI: Tinnitus Handicap Inventory, THQ: Tinnitus Handicap Questionnaire, CI: cochlear implant

The spread of both the postoperative THI and THQ scores was large. Thirteen out of 19 patients (68%, grey patient numbers in table 1) experienced a reduction of their tinnitus in one or more stimulus conditions. Eight participants out of 19 (42%) reported an increase of tinnitus loudness in at least one stimulus condition. There were no significant differences in the postoperative THI and THQ scores between patients with a decrease of tinnitus (THI 36.2, SD 23.1, THQ 49.5, SD 21.3) with single-electrode stimulation and the patients without a decrease of tinnitus (THI 23.5, SD 18.4, THQ 31.5, SD 28.9) with single electrode stimulation. Three out of the four patients with an Advanced Bionics implant and 10 of the 15 patients who used a Cochlear implant, experience a decrease of tinnitus with single-electrode stimulation. Five out of the eight patients with no anamnestic effect on their tinnitus of full-array stimulation, as determined by questionnaire, experienced tinnitus reduction of single-electrode stimulation. Three of the five patients with an overall increase of tinnitus by full-array stimulation experienced tinnitus reduction from single electrode stimulation. Thus, some patients who experienced no effect or even a negative effect of anamnestic full-array stimulation on tinnitus experienced a positive effect of single-electrode stimulation on tinnitus.

Figure 2 shows all individual patient traces together with a mean trace for all conditions at the C-level. Only the C-level results are shown, since these gave the most obvious results, i.e. were obtained by stimulation at moderate intensity. To produce the traces, we calculated three mean VAS values; one for the measurements before stimulation, one for the measurements during the stimulation and one for the measurements after stimulation. The mean effect for all stimuli is shown to be minimal. Stimulation of the apical electrode with medium and high pulse rates showed the most prominent effects.

For the various stimulus conditions, figure 3 shows the number of patients for whom tinnitus decreased, remained unchanged or increased. Altogether, a reduction of the tinnitus amplitude of at least 1 point on the VAS was observed in 24% of the stimulus presentations. The size of the changes was generally small, and never exceeded 3 points on the VAS scale. A tinnitus reduction was more commonly observed when stimulation was at the moderate intensity level (30% of stimulus conditions) compared to stimulations at the low intensity level (18%) (χ^2 (1, N = 222) = 14.115, $p < 0.01$). Tinnitus reduction was also more commonly observed when stimulation was at medium (26%) or high (29%) pulse rates compared to stimulation with low (16%) pulse rates, but this effect was not significant (χ^2 (2, N = 222) = 1.413, $p = 0.493$). Concerning the location of the stimulation, stimulation at apical electrodes (29%) more often resulted in a positive effect compared to stimulation at basal electrodes (19%), which, again, was not a significant difference (χ^2 (1, N = 222) = 0.136, $p = 0.712$).

Figure 2. Patient response traces together with a mean trace for all stimuli at C level. Each thin line represents the result for an individual subject. The thick line shows the mean across subjects. The Y-axis represents the mean tinnitus VAS and the X-axis represents the phases during the experiment: pre-stimulus, during stimulus and post-stimulus.

Figure 3. The number of patients who perceived an increase or decrease of the tinnitus loudness for each of the stimulus conditions.

DISCUSSION

This study examined the acute effect of single-electrode stimulation via a CI on tinnitus. For most stimulus conditions, patients did not experience any change in their tinnitus and the effects of single-electrode stimulation on tinnitus varied substantially across patients. A systematic evaluation of the dependence of tinnitus suppression on the rate, amplitude, or cochlear location of the stimulus showed a significant effect of amplitude only, in that stronger electrical stimulation tended to result in greater tinnitus suppression.

In our study, a reduction of at least 1 point on the VAS was observed in 24% of the stimulus presentations. Within these 24%, the size of the changes was in general small and never exceeded 3 points on the VAS. The VAS is a clinical measuring scale that has been established as valid and reliable in a range of clinical and research applications. [Wewers, and Lowe, 1990] Thus the question arises as to how reliable and reproducible these changes are. In this respect, most patients who indicated that there was a tinnitus reduction, also indicated this reduction to be consistent during the whole stimulus and even after the stimulus. To filter out small, inconsistent and irrelevant changes, we calculated a mean VAS score for the period pre-, during, and after the stimulus.

Several studies examined the effects of electrical stimulation through a CI on tinnitus using stimuli that did not encode environmental sounds. There are four major studies that performed experiments similar to ours.

The first, by Rubinstein et al in 2003 [Rubinstein et al., 2003] presented high-rate pulse train stimuli at various stimulus intensities to three CI patients. In one of these three patients, stimulation had no effect on the tinnitus. In one patient, tinnitus was only suppressed during the stimulus, and a further patient showed suppression of tinnitus during, as well as after the stimulus.

The second study by Chang et al in 2012 [Chang, and Zeng, 2012] used multiple electrical stimuli in 13 CI patients. These stimuli differed in pulse rate, place of stimulation, and level of stimulation. Their most important finding was that the effect of electrical stimulation from a cochlear implant is very subject-specific and that regardless of the kind of stimulus some subjects were more sensitive for experiencing tinnitus reduction. In addition, they found that louder stimuli more often produced a positive effect compared to softer or sub-threshold stimuli. There was also a small effect showing that loud sounds produced by a higher pulse rate give more positive results compared to loud sounds from low pulse rates.

In a third study, Arts et. al. in 2015 [Arts et al., 2015b] presented electrical stimuli in the cochleae of 10 CI patients. The stimuli differed in amplitude, location, modulation, polarity and stimulation rate. They also found that the effect of CI electrical stimulation on tinnitus was subject specific and that stimulations that caused a medium to loud sound more often resulted in a positive effect. Furthermore, they found no relationship between the effect of full-length electrical stimulation, i.e. encoding speech, on tinnitus on the one hand and the effect of electrical stimulation with single electrode stimulation or stimulation with looped patterns, i.e. without encoding speech, on the other.

The final study by Kleine Punte et. al. used 7 subjects with severe unilateral sensorineural hearing loss and implanted with a CI, because of tinnitus. In the first weeks after implantation, they only activated the most basal electrodes and found no significant tinnitus reduction. Tinnitus reduction only occurred when all electrodes were activated [Kleine Punte et al., 2013]. In line with these results, we also found smaller tinnitus reduction from stimulation at the basal electrodes compared to stimulation at the apical electrodes.

Altogether, the results from all studies are compatible with our results; the effect of single-electrode stimulation through a CI on tinnitus is subject specific, is not related to the effect of full-length stimulation through a cochlear implant, and stimulation with higher amplitudes more often results in a positive effect on tinnitus.

The fact that stimuli with a larger amplitude more often cause a positive effect on tinnitus suggests that the tinnitus reduction is generally based on masking, similar to the way in which acoustic tinnitus maskers can mask tinnitus. The sound introduced by the cochlear implant can reduce the contrast between the tinnitus signal and the background activity in the auditory system, with a decrease of the patients' perception of their tinnitus [Vernon, 1977]. Obviously, a stimulus with a relatively large amplitude will not result in complete silence. The maximum effect of such a stimulus is to replace the tinnitus percept by the perception of the masking sound. Thus the aim of a masking therapy can be to establish an overall sound percept that a patient finds more acceptable than the tinnitus alone [Vernon, and Meikle, 2003].

In our study, we investigated the acute effects of single-electrode stimulation on tinnitus. The effects were rather small and not correlated with the effect of the CI on tinnitus in daily life. In other words, there is a difference between the acute effects as observed in the current experiments and the chronic effects on tinnitus by daily use of the CI. Arts et. al.

found that a tinnitus-reducing stimulation pattern added to a speech-coding stimulation strategy can be implemented without adverse effects on speech discrimination [Arts et al., 2016]. To establish whether single-electrode stimulation may also have a similar clinical benefit on tinnitus, chronic studies with long term single-electrode stimulation would be required.

CONCLUSION

Single-electrode stimulation through a CI can ameliorate tinnitus in some implant users. Chronic studies would be required to establish the benefit of such an approach for tinnitus suppression. Such studies would presumably explore single-electrode stimulation for tinnitus suppression combined with full-electrode stimulation for speech comprehension.

REFERENCES

- Akdogan O, Ozcan I, Ozbek C, Dere H: Tinnitus after cochlear implantation. *Auris Nasus Larynx* 2009; DOI: 10.1016/j.anl.2008.04.005
- Aran JM, Cazals Y: Electrical Suppression of Tinnitus; in : Tinnitus. 2008. DOI: 10.1002/9780470720974.ch13
- Arts RAGJ, Georde EL, Griessner A, Zierhofer C, Stokroos RJ: Long-term effects of intracochlear electrical stimulation with looped patterns on tinnitus: A case study. *Ear, Nose Throat J* 2016; DOI: 10.1111/1462-2920.12387
- Arts RAGJ, George ELJ, Chenault MN, Stokroos RJ: Optimizing intracochlear electrical stimulation to suppress tinnitus. *Ear Hear* 2015a; DOI: 10.1097/AUD.0000000000000090
- Arts RAGJ, George ELJ, Griessner A, Zierhofer C, Stokroos RJ: Tinnitus suppression by intracochlear electrical stimulation in single-sided deafness: A prospective clinical trial - Part i. *Audiol Neurotol* 2015b; DOI: 10.1159/000381936
- Arts RAGJ, George ELJ, Stokroos RJ, Vermeire K: Review: Cochlear implants as a treatment of tinnitus in single-sided deafness. *Curr Opin Otolaryngol Head Neck Surg* 2012; DOI: 10.1097/MOO.0b013e3283577b66
- Bovo R, Ciorba A, Martini A: Tinnitus and cochlear implants. *Auris Nasus Larynx* 2011; DOI: 10.1016/j.anl.2010.05.003
- Chang JE, Zeng F-G: Tinnitus suppression by electric stimulation of the auditory nerve. *Front Syst Neurosci* 2012; DOI: 10.3389/fnsys.2012.00019
- Dobie RA, Hoberg KE, Rees TS: Electrical Tinnitus Suppression: A Double-Blind Crossover Study. *Otolaryngol Neck Surg* 1986; DOI: 10.1177/01945998860953P110
- Graham JM, Hazellf JWP: Electrical stimulation of the human cochlea using a transtympanic electrode. *Br J Audiol* 1977; DOI: 10.3109/03005367709078834
- Van De Heyning P, Vermeire K, Diebl M, Nopp P, Anderson I, De Ridder D: Incapacitating unilateral tinnitus in single-sided deafness treated by cochlear implantation. *Ann Otol Rhinol Laryngol* 2008; DOI: 10.1177/000348940811700903
- Jastreboff PJ, azell JWP: A neurophysiological approach to tinnitus: Clinical implications. *Br J Audiol* 1993; DOI: 10.3109/03005369309077884
- Kleine Punte A, De Ridder D, Van De Heyning P: On the necessity of full length electrical cochlear stimulation to suppress severe tinnitus in single-sided deafness. *Hear Res* 2013; DOI: 10.1016/j.heares.2012.08.003
- Kompis M, Pelizzone M, Dillier N, Allum J, Demin N, Senn P: Tinnitus before and 6 months after cochlear implantation. *Audiol Neurotol* 2012; DOI: 10.1159/000335126
- Konopka W, Zalewski P, Olszewski J, Olszewska-Ziaber A, Pietkiewicz P: Tinnitus suppression by electrical promontory stimulation (EPS) in patients with sensorineural hearing loss. *Auris*

- Nasus Larynx 2001; DOI: 10.1016/S0385-8146(00)00086-9
- Mertens G, Van Rompaey V, Van de Heyning P: Electric-acoustic stimulation suppresses tinnitus in a subject with high-frequency single-sided deafness. *Cochlear Implants Int* 2018; DOI: 10.1080/14670100.2018.1473940
- Mo B, Harris S, Lindbæk M: Tinnitus in cochlear implant patients - A comparison with other hearing-impaired patients. *Int J Audiol* 2002; DOI: 10.3109/14992020209056073
- Di Nardo W, Cantore I, Cianfrone F, Melillo P, Scorpecci A, Paludetti G: Tinnitus modifications after cochlear implantation. *Eur Arch Oto-Rhino-Laryngology* 2007; DOI: 10.1007/s00405-007-0352-7
- OkusaM, ShiraishiT, KuboT, MatsunagaT: Tinnitus suppression by electrical promontory stimulation in sensorineural deaf patients. *Acta Otolaryngol* 1993; DOI: 10.3109/00016489309126215
- Pan T, Tyler RS, Ji H, Coelho C, Gehringer AK, Gogel SA: Changes in the tinnitus handicap questionnaire after cochlear implantation. *Am J Audiol* 2009; DOI: 10.1044/1059-0889(2009/07-0042)
- Portmann M, Cazals Y, Negrevergne M, Aran JM: Temporary tinnitus suppression in man through electrical stimulation of the cochlea. *Acta Otolaryngol* 1979; DOI: 10.3109/00016487909126423
- Quaranta N, Fernandez-Vega S, D'Elia C, Filipo R, Quaranta A: The effect of unilateral multichannel cochlear implant on bilaterally perceived tinnitus. *Acta Otolaryngol* 2008; DOI: 10.1080/00016480701387173
- Rubinstein JT, Tyler RS, Johnson A, Brown CJ: Electrical suppression of tinnitus with high-rate pulse trains. *Otol Neurotol* 2003; DOI: 10.1097/00129492-200305000-00021
- Shulman A: External electrical tinnitus suppression: a review. *Am-J-Otol* 1987;
- Tyler RS: Advantages and disadvantages expected and reported by cochlear implant patients. *Am J Otol* 1994;
- Vernon J: Attempts to relieve tinnitus. *J Am Audiol Soc* 1977;
- Vernon JA, Meikle MB: Masking devices and alprazolam treatment for tinnitus. *Otolaryngol Clin North Am* 2003; DOI: 10.1016/S0030-6665(02)00163-9
- Watanabe K, Okawara D, Baba S, Yagi T: Electrocochleographic analysis of the suppression of tinnitus by electrical p... *Audiology* 1997;
- Wewers ME, Lowe NK: A critical review of visual analogue scales in the measurement of clinical phenomena. *Res Nurs Health* 1990;13:227-236.
- Zeng FG, Tang Q, Dimitrijevic A, Starr A, Larky J, Blevins NH: Tinnitus suppression by low-rate electric stimulation and its electrophysiological mechanisms. *Hear Res* 2011; DOI: 10.1016/j.heares.2011.03.010

BRAIN ACTIVITY MEASURED WITH PET IN COCHLEAR IMPLANT PATIENTS WITH TINNITUS

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ABSTRACT

It has become evident from previous studies, that there is both an increase of spontaneous neural activity and cortical reorganisation at several levels in the auditory brainstem and cortex in patients that have hearing loss and tinnitus. Some cochlear implant patients with tinnitus can influence their tinnitus by turning their cochlear implant (CI) on and off. In this study, we aimed to investigate the activity in tinnitus related brain areas in cochlear implant patients with tinnitus. To do this, we used labelled-water ($H_2^{15}O$) PET scans with the CI turned on and off, to examine whether the brain activity corresponds with the patients' subjective tinnitus experience.

Methods

Twelve right handed unilateral cochlear implant recipients were included in this study. They all had received their cochlear implant because of severe bilateral hearing loss and subjective chronic, constant tinnitus for more than 3 months were included in this study. For each subject, 12 labelled-water PET scans were acquired, 6 scans with the cochlear implant on and 6 scans with the implant off. When the cochlear implant was turned on, we presented a free-field 'jungle sounds' masking noise. Before and after every scan, the subject was asked to rate the loudness of the momentary perceived tinnitus on a scale from 0 to 10 (with 0 being very weak and 10 being very strong). We scored a reduction in tinnitus during stimulation if patients subsequently scored their tinnitus at least two points lower on VAS with stimulation compared to the score for VAS without stimulation.

Results

The bilateral auditory cortices were activated by the CI ($p < 0.05$, FWE corrected) in the whole group of subjects. This activation was most prominent on the right side. Dividing the group into subgroups with left-sided CI or right-sided CI resulted in the loss of significant activation of the auditory cortex. The same was the case when we divided the group into subgroups of patients in whom the implant did or did not inhibit the tinnitus during cochlear implant activation.

Discussion/Conclusion

The prominent activation in the right auditory cortex is consistent with the non-language content of the sound stimulus used. We found no significant brain activation or inhibition associated with tinnitus inhibition by the cochlear implant. This could be due to the small number of subjects, or because differences in brain activation are too subtle to be detected by PET-scanning.

INTRODUCTION

Many causes of tinnitus have in common that they accompany peripheral hearing loss, especially high-frequency hearing loss (McCombe et al., 2001; Møller, 2003). A key hypothesis in the pathogenesis of subjective tinnitus is that it arises as a response of the central auditory system to peripheral hearing loss (Eggermont & Komiya, 2000; Kaltenbach, 2006; Moffat et al., 2009). Peripheral hearing loss results in a decrease of afferent input to the brainstem. This may result in an increase of spontaneous neural activity at several levels in the auditory brainstem and cortex, which is believed to potentially underlie tinnitus (Kaltenbach, 2006; Moffat et al., 2009). In lab animals, this increase in spontaneous activity has been shown to occur quickly after noise trauma, and become larger in the weeks or months after sensory deafferentation (Eggermont & Komiya, 2000).

The past two decades have seen an increase in studies of brain activity in human tinnitus patients. For this, different imaging methods such as EEG, MEG, PET, and MRI have been applied, to identify brain regions involved in tinnitus. The review by Lanting et al. (2009) summarizes the findings for PET and for functional MRI in tinnitus patients, showing possible changes in all parts of the central auditory system (Lanting, de Kleine, & van Dijk, 2009). Although the general idea is that tinnitus corresponds to enhanced brain activity, findings from these imaging studies are diverse and show few clear outcomes. It is also becoming clear that not only is the central auditory system involved in tinnitus, but also non-auditory structures such as the limbic system, the frontal lobe, and the cerebellum (Langers, D. R. M., & de Kleine, E., 2016).

Cochlear implant patients with tinnitus are interesting to investigate because some of these patients can influence their tinnitus by turning their cochlear implant on, which can partly or even completely weaken the tinnitus. Such patients, perhaps offer greater potential to more clearly examine the brain activity associated with tinnitus.

In this study, we investigated the influence of a cochlear implant on the neural activity in tinnitus-related brain areas by making labelled water ($H_2^{15}O$) PET scans with the cochlear implant switched on or off and observing whether this corresponded with changes in the subjective tinnitus experience of the patients.

METHODS

Ethics approval

The study was approved by the ethics committee of the University Medical Center Groningen and informed consent was obtained from all subjects. This observational case-control study was a collaboration of the departments Otorhinolaryngology and Nuclear Medicine and Molecular Imaging (NMMI) at the University Medical Center Groningen.

Subjects

This study included 12 right-handed, unilateral cochlear implant recipients who received their implant because of severe bilateral hearing loss, but had also suffered from subjective chronic tinnitus for more than 3 months. Patient characteristics are shown in table 1. The patients were 18 years of age or older at the time of the experiment (range 23-83 years) and were implanted at least 6 months before the experiment commenced. Ten patients had received a cochlear implant from the company 'Cochlear' (CI 24R k, CI 24R CA, CI 24R CS, CI24RE CA), and 2 patients from the company 'Advanced Bionics' (Hires 90k, Helix). We included four female and eight male patients.

PET scans

After careful selection and inclusion of patients as described above, the cochlear implant recipients underwent a series of labelled water PET-scans for the objectivation of tinnitus-related neural activity in the central nervous system. As a tracer to measure regional cerebral blood flow, we used ($H_2^{15}O$) (half-life 122 sec). A Siemens Ecat Exact HR+ PET scanner was operated in three-dimensional mode, with a 15,5 cm axial field of view and acquired 63 slices simultaneously. Each scan was performed after an intravenous bolus injection of 500 MBq of ($H_2^{15}O$) per scan. To account for background activation, scanning started 30 s prior to injection and continued for 120 seconds. Between two successive scans, there was a 10-minute interval, allowing for decay of the radioactive tracer.

Procedure

For each subject, 12 PET scans were acquired, 6 scans with the cochlear implant on and 6 scans with the implant off. One patient could not tolerate the full length of the experiment, and here only 11 scans were made; 6 scans with the cochlear implant on and 5 scans with the implant off. Immediately after every scan, the speech processor of the cochlear implant was alternately turned on and off from scan to scan by the researcher, starting with the implant turned on. The total measurement time per subject was 134 minutes: this included twelve scans (of 120 s each) plus 11 interscan intervals (of 10 min).

Table 1: patient characteristics and in the right most columns the VAS scores

Patient number	Gender	Age (years)	Phoneme score (% correct)	Implant type	Side of cochlear implant	Mean VAS with CI on (range)	Mean VAS with CI off (range)
<u>1</u>	Female	38	83	Cochlear CI24R CS	Left	5 (5-5)	5 (4-5)
<u>2</u>	Male	23	45	Advanced Bionics HiRes 90K Helix	Left	2 (0-3)	2.5(2-3)
<u>3</u>	Male	76	83	Cochlear CI24R CA	Left	5 (4-6)	6 (5-7)
<u>4</u>	Male	41	60	Cochlear CI24RE CA	Right	5.5 (5-6)	5.5 (5-6)
<u>5</u>	Male	unknown	unknown	Advanced Bionics HiRes 90K Helix	Right	7 (7-8)	7 (7-8)
<u>6</u>	Female	63	unknown	Cochlear CI24R CS	Right	1 (1-2)	3.5 (3-4)
<u>7</u>	Female	unknown	unknown	Cochlear	Right	8 (8-8)	8 (7-8)
<u>8</u>	Male	83	43	Cochlear CI24R k	Left	0 (0-0)	2 (1-3)
<u>9</u>	Male	62	79	Cochlear CI24RE CA	Right	4 (4-4)	4 (4-4)
<u>10</u>	Female	unknown	unknown	Cochlear	Left	0 (0-0)	8 (7-8)
<u>11</u>	Male	unknown	unknown	Cochlear	Right	4 (4-5)	7 (6-7)
<u>12</u>	Male	57	80	Cochlear CI24R CS	Right	0 (0-0)	5 (4-5)

The bold and underlined patient numbers are the patients with tinnitus inhibition during activation of the cochlear implant; the phoneme scores are the maximum phoneme scores with the cochlear implant

When the cochlear implant was turned on, we presented a free-field ‘jungle sounds’ stimulus to activate the implant (Jungle Relax With Nature Vol. 16 01 Jungle). Before and after each scan, the subject had to rate the momentary loudness of the perceived tinnitus on a scale from 0 to 10 (with 0 being very weak and 10 being very strong). We scored tinnitus as being reduced during stimulation if patients subsequently scored their tinnitus at least two points lower on VAS with stimulation compared to the score for VAS without stimulation. Five of the 12 patients experienced significant tinnitus reduction while the cochlear implant was on (**bold and underlined patient numbers in table 1**).

Statistical analysis

All data were analyzed using Statistical Parametric Mapping (SPM), version 8 and Matlab 2015a. Preprocessing was performed for each subject. Images were realigned, normalized to the SPM PET template, and smoothed using an 8 mm FWHM kernel.

In SPM, a flexible factorial design was chosen, with the two factors, subject and implant on/off. An interaction between these two factors was defined, allowing assessment of the activation and deactivation for each subject separately. Normalization was implemented with an ANCOVA by subject. Threshold masking was set at the default value of 0.8; voxels with a lower value were deemed extra-cranial. Voxel-wise analyses were performed, contrasting the scans where the CI was on, with the scans where the CI was off. This was carried out both for the whole subject group, as well as for subgroups. The contrast “CI on” > “CI off” will be referred to as brain activation by the CI, whereas contrast “CI on” < “CI off” will be referred to as brain deactivation by the CI.

A second-level analysis was performed to assess differences in activation level between subject groups. For this analysis, the contrast images per subject were used as the input and a two-sided t-test was performed.

Significance levels were set at 0.05, and corrected for family-wise errors (FWE), unless stated otherwise. The SPM Anatomy toolbox was used for determining the anatomic location of the activated brain regions.

RESULTS

For the whole group of subjects, consisting of twelve unilaterally implanted subjects (five left-sided, seven right-sided), the auditory cortices were bilaterally activated by the CI ($p < 0.05$, FWE corrected), see Table 2. This activation was most prominent on the right side. When we divided the group into subgroups with left-sided CI or right-sided CI, the significance of the activation disappeared. The same was the case when we divided the group into subgroups of patients in whom the implant did, or did not, inhibit the tinnitus during CI activation.

Group	Brain region	Cluster size	Peak T-level	MNI Coordinates
All (n=12)	AC left	35	5.79	(-52, -16, 0)
	AC right	149	6.06	(70, -24, 10)

Table 2. Brain activation by the cochlear implant, for all subjects. Column 2: brain regions for which the contrast “CI on>CI off” was significant. Column 3-5: cluster size in number of voxels, peak T-level and corresponding MNI coordinates. AC: Auditory Cortex.

Figure 1 shows the clusters of activation as projected on a T1 MRI template. The activated cluster size in the right hemisphere is 1.9 times the size of the cluster in the left hemisphere.

Brain deactivation by the CI was not significant for the whole subject group, with $p < 0.05$ and correcting for FWE. There was also no significant deactivation for either subgroup.

A second-level analysis was performed to assess differences in activation between subject groups. Comparing the subject groups with and without tinnitus inhibition did not give significant results, with $p < 0.05$ and correcting for FWE. There were also no significant findings in the subgroups with left-sided CI or right-sided CI.

A region-of-interest analysis was performed to assess possible differences between the subject groups who did, or did not, show tinnitus inhibition. The average activation of the bilateral auditory cortices was calculated for each subject. Figure 2 shows this

Figure 1. Brain activation for the whole subject group (n=12), projected on an anatomical MRI template, showing two clusters in the left and right auditory cortices. The significance level was set at $p < 0.05$, FWE corrected.

Figure 2. Average activation of the bilateral auditory cortices, grouped according to tinnitus inhibition. Each point indicates a single subject.

activation, where the subjects with and without tinnitus inhibition are grouped together. The activation of the bilateral auditory cortices was not significantly different between the groups (t-test, $p=0.24$)

DISCUSSION

The aim of the current study was to investigate brain activity associated with tinnitus. Our general approach was to compare PET-scans between conditions in which a cochlear implant was turned on, compared to conditions where the implant was off. In some CI users, turning on the implant provided suppression of tinnitus. Unfortunately, the suppressive effect of cochlear implantation could not be associated with measures of brain activity.

The only significant effect found, was an enhancement of activity in the auditory cortices related to turning on the implant. Clearly, this increase in activity must have been caused

by the auditory stimulus played during the experimental procedures. Responses were most pronounced in the right auditory cortex, consistent with the non-language nature of the stimulus (Lazard et al., 2012; Łukaszewicz-Moszyńska, Lachowska, & Niemczyk, 2014).

When separately analyzing right- and left-implanted participants, activation in the auditory cortices was not significantly different. Hence, we could not confirm earlier reports showing predominant activation in the cortex contralateral (Giraud, 2001; Herzog et al., 1991; Y. Naito et al., 1995; Yasushi Naito et al., 2000) or ipsilateral (Łukaszewicz-Moszyńska et al., 2014; Wong, Miyamoto, Pisoni, Sehgal, & Hutchins, 1999) to the implanted ear.

The two groups in our study, were those that experienced tinnitus suppression by the implant ($n=4$) and those that did not ($n=8$). In neither group was, there significant activation or inhibition due to turning on or off the implant. Hence, determining areas that were specifically associated with tinnitus or tinnitus suppression, was not possible. Note that we did not find significant brain activation in any of the analyses in which small subgroups of subjects were compared (tinnitus suppression vs. no tinnitus suppression, and left-implanted vs. right-implanted). Only when combining all subjects in a single analysis ($n=12$), was brain activity found to be significant. This suggests that the current study uses too few subjects to show subgroup effects.

We may reconsider the specific expectations that were made when planning this study. Firstly, tinnitus, as well as sound-evoked activity, was expected to be localized in the auditory cortex and possibly additional brain areas. Earlier papers (Łukaszewicz-Moszyńska et al., 2014; Wong et al., 1999) showed, with relatively small subject groups, that brain activity due to cochlear implant stimulation can be detected with a PET scanner. Thus, based on the earlier literature, the current number of participants was expected to be sufficient.

Secondly, let us consider the possible effect of turning on the CI, while a sound is being played. In the following, we assume that the tinnitus is either completely suppressed or not affected at all by turning on the implant. For simplicity, we ignore the case in which tinnitus may also be partly suppressed by turning on the implant.

All participants experienced tinnitus when the implant was off, and perceived the sound stimulus when the implant was on. Thus, the auditory cortex was always activated, both with the CI on and off. For participants for whom the CI did not suppress tinnitus, auditory cortex activity would reflect both tinnitus and the sound stimulus. In contrast,

when tinnitus is suppressed by CI activation, auditory cortex activity reflected the sound stimulus only. Thus, by comparing the auditory cortex activity between participants with and without tinnitus suppression, we are essentially contrasting ‘sound-evoked’ and ‘sound-evoked + tinnitus’ activity between subject groups. The absence of a group effect in the second-level analysis that compared participants with and without suppression may imply that this difference is too subtle to be detected by PET-scanning. Larger subject groups may possibly help in detecting a group effect.

CONCLUSION

Water-labelled PET scans in cochlear implant recipients that had tinnitus showed significant activation of the auditory cortices during cochlear implant activation. This cortical activation was most prominent on the right side, consistent with the non-language content of the sound stimulus used. We found no significant brain activation or inhibition associated with tinnitus inhibition due to the cochlear implant.

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REFERENCES

- Eggermont, J. J., & Komiya, H. (2000). Moderate noise trauma in juvenile cats results in profound cortical topographic map changes in adulthood. *Hearing Research*. [https://doi.org/10.1016/S0378-5955\(00\)00024-1](https://doi.org/10.1016/S0378-5955(00)00024-1)
- Giraud, A. L. (2001). Functional plasticity of language-related brain areas after cochlear implantation. *Brain*. <https://doi.org/10.1093/brain/124.7.1307>
- Herzog, H., Lamprecht, A., Kühn, A., Roden, W., Vosteen, K. H., & Feinendegen, L. E. (1991). Cortical activation in profoundly deaf patients during cochlear implant stimulation demonstrated by h215o pet. *Journal of Computer Assisted Tomography*. <https://doi.org/10.1097/00004728-199105000-00005>
- Kaltenbach, J. A. (2006). Summary of evidence pointing to a role of the dorsal cochlear nucleus in the etiology of tinnitus. In *Acta Oto-Laryngologica*. <https://doi.org/10.1080/03655230600895309>
- Langers, D. R. M., & de Kleine, E. (2016). Tinnitus Neurophysiology According to Structural and Functional Magnetic Resonance Imaging. In P. van D. In A. T. Cacace, E. de Kleine, A. G. Holt (Ed.), *Scientific Foundations of Audiology. Perspectives from Physics, Biology, Modeling, and Medicine* (pp. 351–369). Plural Publishing.
- Lanting, C. P., de Kleine, E., & van Dijk, P. (2009). Neural activity underlying tinnitus generation: Results from PET and fMRI. *Hearing Research*. <https://doi.org/10.1016/j.heares.2009.06.009>
- Lazard, D. S., Vincent, C., Venail, F., van de Heyning, P., Truy, E., Sterkers, O., ... Blamey, P. J. (2012). Pre-, Per- and Postoperative Factors Affecting Performance of Postlinguistically Deaf Adults Using Cochlear Implants: A New Conceptual Model over Time. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0048739>
- Łukaszewicz-Moszyńska, Z., Lachowska, M., & Niemczyk, K. (2014). Auditory cortical activation and plasticity after cochlear implantation measured by PET using fluorodeoxyglucose. *Functional Neurology*. <https://doi.org/10.11138/FNeur/2014.29.2.121>
- McCombe, A., Baguley, D., Coles, R., McKenna, L., McKinney, C., & Windle-Taylor, P. (2001). Guidelines for the grading of tinnitus severity: The results of a working group commissioned by the British Association of Otolaryngologists, Head and Neck Surgeons, 1999. *Clinical Otolaryngology and Allied Sciences*. <https://doi.org/10.1046/j.1365-2273.2001.00490.x>
- Moffat, G., Adjout, K., Gallego, S., Thai-Van, H., Collet, L., & Noreña, A. J. (2009). Effects of hearing aid fitting on the perceptual characteristics of tinnitus. *Hearing Research*. <https://doi.org/10.1016/j.heares.2009.04.016>
- Møller, A. R. (2003). Pathophysiology of tinnitus. *Otolaryngologic Clinics of North America*. [https://doi.org/10.1016/S0030-6665\(02\)00170-6](https://doi.org/10.1016/S0030-6665(02)00170-6)
- Naito, Y., Okazawa, H., Honjo, I., Takahashi, H., Kawano, M., Ishizu, K., & Yonekura, Y. (1995). Cortical activation during sound stimulation in cochlear implant users demonstrated by

positron emission tomography. In *Annals of Otolaryngology, Rhinology and Laryngology*.

Naito, Yasushi, Tateya, I., Fujiki, N., Hirano, S., Ishizu, K., Nagahama, Y., ... Kojima, H. (2000).

Increased cortical activation during hearing of speech in cochlear implant users. *Hearing Research*. [https://doi.org/10.1016/S0378-5955\(00\)00035-6](https://doi.org/10.1016/S0378-5955(00)00035-6)

Wong, D., Miyamoto, R. T., Pisoni, D. B., Sehgal, M., & Hutchins, G. D. (1999). PET imaging of cochlear-implant and normal-hearing subjects listening to speech and nonspeech. *Hearing Research*. [https://doi.org/10.1016/S0378-5955\(99\)00028-3](https://doi.org/10.1016/S0378-5955(99)00028-3)

8

GENERAL DISCUSSION AND CONCLUSION

In the majority of implant recipients, cochlear implantation has a positive effect on tinnitus, both in recipients with severe bilateral hearing loss as well as in the population of patients with single-sided deafness. However, in a small group of patients, the tinnitus worsens after implantation. Previous studies describe suppression of tinnitus in 52-89% of the cases (Bovo, Ciorba, & Martini, 2011; Kompis et al., 2012; Pan et al., 2009). An exacerbation or onset of tinnitus has only been described in 1-10% and 0-23.5% respectively (Akdogan et al., 2009; Baguley & McFerran, 2002; Bovo et al., 2011; Kompis et al., 2012; Quaranta et al., 2004). In the patients whose tinnitus still existed after cochlear implantation, the tinnitus handicap was generally small. As mentioned in the introduction, this thesis aimed to obtain more insight into the number of tinnitus patients that may benefit from cochlear implantation within the population of patients that have severe binaural sensorineural hearing loss. We tried to clarify the preoperative factors that can predict the outcome of cochlear implantation on tinnitus. We also explored single-electrode stimulation strategies that aim to reduce tinnitus perception. Furthermore, we tried to measure central nervous system changes that may be associated with tinnitus reduction in cochlear implant recipients.

In the following text the main findings and potential future implications will be discussed and ideas for future research are presented.

Questionnaire outcomes: comparison between prospective and retrospective studies

Our retrospective questionnaire study, in Chapter 3, described an improvement of tinnitus (tinnitus reduction or cessation) in 56% of the patients that had had pre-operative tinnitus. On the other hand, this study described a worsening of tinnitus in 8% of the patients with preoperative tinnitus and an onset of tinnitus in 20% of the patients who had had no preoperative tinnitus. Our prospective questionnaire study, in Chapter 5, described tinnitus cessation in 28%, of the cases and tinnitus improvement in approximately 75% of the cases. In this latter study, none of the patients experienced tinnitus onset. These numbers are compatible with the many questionnaire studies that have already been published on this subject.

The numbers of our prospective and retrospective questionnaire study are somewhat different. A lot of questionnaire studies have already been published concerning the effect of cochlear implantation on tinnitus, both in a retrospective and a prospective setting. We were therefore interested to study whether these large numbers of questionnaire studies also showed differences between the outcome of the questionnaires studies carried out in a retrospective manner compared to prospective studies.

A comparison shows that in the retrospective studies, somewhat more patients experienced tinnitus deterioration and onset compared to the prospective studies (table 1). Furthermore, prospective studies showed slightly more patients with tinnitus reduction or elimination. In the future it would be useful to do a detailed meta-analysis on these data, to see whether there are significant differences between questionnaire studies with a prospective and retrospective design.

There are three factors concerning the design of the study that can influence the outcomes of questionnaire studies: 1. Recall bias, 2. Social desirability and effort justification and 3. Response shift. These three possible confounders have to be taken into account when comparing the results of prospective and retrospective questionnaire studies.

The first confounder is recall bias. When the study is carried out retrospectively, there may be a long time between implantation and questionnaire completion. This may incur a bias that is caused by patients not remembering the situation before the intervention very well at the time the questionnaires are filled in. This could magnify the effects, because patients with a positive or negative effect of implantation on tinnitus may remember the situation before implantation respectively worse or better than it actually was, resulting in an overestimation of the positive or negative effect of cochlear implantation.

The second confounder of a retrospective design is a potential bias due to social desirability and effort justification, causing a tendency for patients wanting to fulfill the expectation of the researchers. This may enhance the positive effect of cochlear implantation on tinnitus.

A third possible confounder, concerning a prospective design, is response shift, because the questionnaires are filled in at different times. Response shift occurs due to the time lag between the time points at which the questionnaires are completed. Response shift means that, over time, people tend to change their internal standards or values of how they function (Schwartz, Andresen, Nosek, & Krahn, 2007). Normally, people adapt to the impairments they have, such as hearing loss. After something has changed in their health situation (for example after CI implantation), they function at a new (higher) level, which causes them to re-evaluate their health situation and to reset the internal standard of their health condition. In a prospective study, the adaptational processes between the first and second assessment can cause changes in patients' quality of life evaluations, thereby giving an underestimation of the actual change between pre- and post-test (Schwartz et al., 2007; Visser, Oort, & Sprangers, 2005).

Table 1: retrospective and prospective questionnaire studies concerning the effect of cochlear implantation on tinnitus											
Study	Year	Sample size (n)	Preoperative tinnitus (n)	Study design	Eliminated (n)	Improved (n)	Unchanged (n)	Deterioration (n)	Onset (n)	Preop handicap	Postop handicap
Amoodi	2011	142	142 (100%)	Prospective	53 (37.3%)	41 (28.9%)	41 (28.9%)	7 (4.9%)	-	THI 36.2	THI 20.2 (p<0.001)
Boxo	2011	51	36 (70.6%)	Prospective	13 (38.1%)	15 (41.7%)	6 (16.7%)	2 (5.5%)	-	THI 45.8	THI 32.3 (p<0.001)
Denajumdar	1999	99	80 (80.1%)	Prospective	62 (77.5%)	-	18 (22.5%)	-	-	-	-
Di Nardo	2007	30	20 (66.7%)	Prospective	8 (40.0%)	6 (30.0%)	5 (25.0%)	1 (5.0%)	-	THI 44.5	THI 25.0 (p<0.05)
Gremel	2003	39	26 (66.7%)	Prospective	4 (15.4%)	7 (26.9%)	13 (50.0%)	2 (7.7%)	2 (5.1%)	-	-
Ito	1997	60	54 (90.0%)	Prospective	-	50 (92.6%)	4 (7.4%)	-	-	-	-
Kim	2013	35	22 (62.9%)	Prospective	10 (45.5%)	12 (34.5%)	-	-	-	THI 50.5	THI 10.1 (p<0.001)
Kleine Punte	2011	26	26 (100%)	Prospective	3 (11.5%)	23 (88.5%)	-	-	-	TQ 60	TQ 31 (p<0.001)
Kloostra	2017	44	29 (65.9%)	Prospective	8 (27.6%)	-	21 (72.4%)	-	0 (0%)	THI 23.6	THI 13.3
Kompis	2012	174	125 (71.8%)	Prospective	25 (20.0%)	64 (51.2%)	27 (21.6%)	9 (7.2%)	5 (2.9%)	THQ 30.7	THQ 20.9
Pan	2009	244	153 (62.7%)	Prospective	94 (61.4%)	59 (38.6%)	-	-	11 (4.5%)	THQ 41.2	THQ 29.8 (p<0.001)
Ruckenstein	2001	38	38 (100%)	Prospective	17 (44.7%)	19 (50.0%)	2 (5.3%)	-	-	-	-
Tao	2012	48	16 (33.3%)	Prospective	6 (37.5%)	1 (6.3%)	9 (56.3%)	-	2 (4.2%)	-	-
Van de Heyning	2008	22	-	Prospective	-	-	-	-	-	TQ 58.4	TQ 33.3 (p<0.001)
Van Zon	2016	38	16 (42.1%)	Prospective	4 (25.0%)	12 (75.0%)	-	-	6 (15.8%)	THI 13.0	THI 3.0 (p<0.01)
Wang	2015	33	33 (100%)	Prospective	-	27 (81.9%)	6 (18.2%)	-	-	THI 56.4	THI 24.7 (p<0.05)
Daneshi	2005	20	20 (100%)	Retrospective	11 (55%)	5 (25%)	4 (20%)	-	-	TQ 52.3	TQ 35.6 (p<0.001)
Kloostra	2015	152	76 (50.0%)	Retrospective	14 (18.4%)	26 (34.2%)	29 (38.2%)	7 (9.2%)	11 (14.4%)	THI 30.2	THI 22.3 (p<0.05)
McKerrow	1991	6	6 (100%)	Retrospective	5 (83.3%)	-	1 (16.7%)	-	-	THQ 40.4	THQ 31.8 (p<0.01)
Sladen	2016	23	13 (56.5%)	Retrospective	-	12 (92.3%)	1 (7.7%)	-	-	-	-
Souliere	1992	33	28 (84.8%)	Retrospective	-	15 (53.6%)	12 (42.6%)	1 (3.6%)	-	-	-
Yonehara	2006	29	21 (72.4%)	Retrospective	7 (33.3%)	8 (38.1%)	3 (14.3%)	3 (14.3%)	-	-	-
Mean Prospective/Retrospective		577 (59%/138 (66%) (excl. 100%))			307 (37%/37 (26%))	336 (40%/66 (46%))	146 (17%/17 (12%))	21 (3%/11 (8%))	26 (3%/11 (8%))	THI 38.6/30.2 TQ 59.2/52.3 THQ 36.0/40.4	THI 18.4/22.3 TQ 32.2/35.6 THQ 25.4/31.8

The confounders of prospective and retrospective designs could cause the effects of retrospective studies to be more magnified compared to the effect of the prospective studies. In science, prospective questionnaire studies are often preferred, and if a significant effect is found in prospective studies it is likely that there is actually an effect present. However, to measure the contentment of patients concerning an intervention, it may also be useful to use a retrospective questionnaire study. In that way, patients can compare their feelings about the present situation with their feelings before the intervention. For the future it would be interesting to perform a prospective as well as a retrospective questionnaire study with the same patients on the same subject to study if the outcomes are different between the prospective and retrospective design and what the effects of response shift are.

Informing the cochlear implant candidate

Besides preoperatively informing the cochlear implant candidate about the effect of the implantation on their hearing ability, it is also important to pay attention to the presence of tinnitus in these patients. If tinnitus is present, it is also important to know how much the tinnitus affects the quality of life of the patient. Therefore, I believe it is valuable that every cochlear implant candidate completes at least a tinnitus handicap questionnaire before the operation. There are multiple tinnitus questionnaires available: the Tinnitus Questionnaire (TQ/mini-TQ) (Goebel & Hiller, 1994), the Tinnitus Handicap Inventory (THI) (Newman, Jacobson, & Spitzer, 1996), the Tinnitus Handicap Questionnaire (THQ) (Kuk, Tyler, Russell, & Jordan, 1990) and the Tinnitus Functional Index (TFI) (Meikle et al., 2012). Furthermore, there is the Tinnitus Reaction Questionnaire (TRQ) (Wilson, Henry, Bowen, & Haralambous, 1991), but this questionnaire is not validated for the Dutch language.

In addition, it is important to inform every cochlear implant candidate about the different outcomes of cochlear implantation on tinnitus. As a rule of thumb clinicians can inform their patients that about 75% of the cochlear implant patients with preoperative tinnitus experience improvement of the tinnitus after the implantation. About 15% show no effect of cochlear implantation on tinnitus and 5 to 10% show deterioration of the tinnitus after implantation (see table 1). It is also important to mention to the patients without preoperative tinnitus that there is about 5 to 10% chance of tinnitus onset after cochlear implantation (Akdogan et al., 2009; Bovo et al., 2011; Klooststra et al., 2015; Klooststra et al., 2019; Kompis et al., 2012; Pan et al., 2009; Quaranta et al., 2004; Rubinstein, Tyler, Johnson, & Brown, 2003).

The results of previous studies concerning predictors of a positive or negative effect of cochlear implantation on tinnitus are diverse and inconsistent. They describe less preoperative hearing loss, a higher preoperative tinnitus handicap, fewer years of hearing loss and tinnitus prior to implantation, and a higher age at implantation as possible predictors of both a positive and a negative effect of implantation on tinnitus (Kompis et al., 2012; Olze et al., 2011; Pan et al., 2009; Souliere, Kileny, Zwolan, & Kemink, 1992). Besides these studies, Pan et al. found a higher preoperative hearing handicap to be a predictor of a positive effect of cochlear implantation on tinnitus and a higher additional hearing loss after implantation to be a predictor of a negative effect on tinnitus (Pan et al., 2009). In our study described in Chapter 4, in which we performed logistic regression analyses using possible preoperative predictors and the effect on tinnitus as outcome measure, it was not possible to create a significant model to predict a positive effect of cochlear implantation on tinnitus. However, we found a low preoperative tinnitus handicap and a low preoperative hearing handicap to be predictors for a negative effect of cochlear implantation on tinnitus. Therefore, as concluded from this study, in the preoperative assessment of the cochlear implant candidate, my advice would be to not only administer a tinnitus handicap questionnaire, but also the APHAB (Abbreviated Profile of Hearing Aid Benefit) (Cox & Alexander, 1995). In general, the better the preoperative situation of the patient, with regard to tinnitus handicap and hearing handicap, the more chance there is of a negative effect of the cochlear implantation on postoperative tinnitus. In the future, it would be worthwhile to carry out further research concerning preoperative predictors of the effect of cochlear implantation on tinnitus, preferably in a large prospective study, to gain more information for clinical decision making and pre-operative patient counselling.

After cochlear implantation, it is important to evaluate the presence of tinnitus and the effects of tinnitus on daily life. If the tinnitus is still problematic after implantation, it is worth trying different stimulation strategies through the cochlear implant aiming for tinnitus reduction. These stimulation strategies could be added as a tinnitus suppression combined with full-electrode stimulation for speech comprehension in patients who do not experience tinnitus reduction by full-electrode stimulation alone. This extra stimulation strategy can function as a tinnitus masking therapy (J. A. Vernon & Meikle, 2003). From previous studies, and from our systematic evaluation of the dependence of tinnitus suppression on the rate, amplitude and cochlear location of the stimulus (Chapter 6), we know that the effect of single-electrode stimulation through a CI on tinnitus is subject specific, is not related to the effect of full-length stimulation, and that stimulation with higher amplitudes more often results in a positive effect on tinnitus (Arts et al. 2015; Arts et al., 2015; Chang & Zeng, 2012; Kleine Punte et al., 2013; Rubinstein et al., 2003). This

is why, in patients who have problematic tinnitus after implantation, in addition to full-length stimulation for speech comprehension, different stimulation strategies with higher amplitudes as a tinnitus masking therapy are worth trying.

Long-term studies would be required to establish the benefit of a tinnitus masking sound for tinnitus suppression through a cochlear implant. Such studies would presumably explore (single)electrode stimulation for tinnitus suppression combined with full-electrode stimulation for speech comprehension. In future studies, the masking sound through the cochlear implant can be a broad spectrum of white noise or can be focused on the frequency band of the patient's tinnitus. The kind of stimulus that is presented to the patients can be based on psychoacoustic methods, such as sound matching, pitch matching, loudness matching and minimum masking level. Previous studies suggest that masking sounds would not negatively influence the patient's speech discrimination (Arts et al. 2015). The effect of the stimulus on tinnitus could be evaluated using a visual analogue scale (VAS), or by tinnitus handicap questionnaires. The follow up should be after at least 12 months, because previous studies of regular sound therapy show that the largest effect of sound therapy on tinnitus is seen in the first 3 months. After that, the positive effect seems to diminish (Davis, Paki, & Hanley, 2007; Henry et al., 2008).

Mechanisms of the effect of cochlear implantation on tinnitus

As mentioned in Chapter 2, a number of mechanisms have been proposed to explain the beneficial effect of cochlear implantation on tinnitus. The three most frequently mentioned mechanisms are: 1. Tinnitus reduction by masking the tinnitus with an external sound, 2. Tinnitus reduction by plastic reorganisation of the central auditory system, and 3. Tinnitus reduction by psychological effects of the major surgical intervention (Bovo et al., 2011; Festinger, 1961; Quaranta et al., 2004).

In the stimulation study, described in Chapter 6, we tested the effect of the cochlear implant on tinnitus immediately after stimulating through the cochlear implant. Thus, in this study we tested the first mechanism; tinnitus reduction by masking using an external sound. We found that stimuli with a larger amplitude more often caused a positive effect on tinnitus. This confirms the theory that tinnitus reduction through a short-term electric stimulus is most often based on masking by an external sound. The sound introduced by the cochlear implant can reduce the contrast between the tinnitus signal and the background activity in the auditory system, and thus a decrease of the patients' perception of their tinnitus (J. Vernon, 1977). Obviously, a stimulus with a relatively large amplitude, will not result in complete silence. The maximum effect of such a stimulus is to replace the tinnitus percept

with the perception of the masking sound. So, the aim of a masking therapy can be to establish an overall sound percept that a patient finds more acceptable than the tinnitus alone (J. A. Vernon & Meikle, 2003). It could be that when a long-term (at least 6 months) electric stimulus through the cochlear implant is given, a tinnitus reduction by plastic reorganization by the central auditory system may result. Perhaps, in this situation, we could also find tinnitus reduction by sub-threshold stimuli.

In the H_2O^{15} PET study, described in Chapter 7, we looked at the activation of the central auditory system immediately after switching the cochlear implant on and off. We tested the effect on tinnitus of stimulation on the central nervous system immediately after giving an electric stimulus through the cochlear implant. Thus, in this study we tested the first mechanism again; tinnitus reduction by masking the tinnitus with an external sound. However, our PET study probably was underpowered, and perhaps because of this we did not find significant differences in activation between patients with and without tinnitus reduction immediately after switching on the cochlear implant. Although previous studies describe a tinnitus reduction by masking, this does not necessarily cause plastic reorganization of the central auditory system. In the future, it may be better to perform a PET scan study in patients who describe tinnitus reduction that only develops months after the implantation, and compare these patients to those who do not experience this tinnitus reduction during the months following implantation.

The second mechanism; tinnitus reduction by plastic reorganization of the central auditory system was not tested as part of this thesis. Plastic reorganization of the central auditory system presumably takes at least 6 months to develop. This mechanism could play a role in patients who experience tinnitus reduction over several months after implant activation.

The third mechanism; a post-implantation tinnitus reduction caused by psychological mechanisms, would occur in the first months after the operation. The major surgical procedure, and the positive postoperative expectations concerning tinnitus, may induce a subjective outcome of this major investment that is more positive than it actually is. This is the so-called effort justification. This was also mentioned in the discussion of Chapter 3 of the retrospective questionnaire study we carried out. This mechanism is in agreement with the cognitive dissonance theory of Festinger. This theory assumes that opposing cognitions and experiences create tensions and dissonances that are undesirable (Festinger, 1962). Unconsciously, people try to avoid this tension and dissonance. If one made a great effort for something that one afterwards did not like, this creates cognitive dissonance. In

these situations, one is unconsciously inclined to evaluate this situation more positively than it actually is. There are many studies that described people experiencing a more positive outcome when they make a great investment (financial or in effort such as for a cochlear implantation) than it actually is. The effect of effort justification was probably also instrumental in the questionnaire studies we performed, since the positive effects of cochlear implantation on tinnitus are magnified in the retrospective questionnaire study compared to the results of the prospective questionnaire study.

Future perspectives

From this thesis can be concluded that the prevalence of tinnitus in the population of cochlear implant candidates is relatively high. In only a small part of this population the tinnitus is severe. The first step for future research would be to perform a pre- and postoperative tinnitus handicap questionnaire and hearing handicap questionnaire on all cochlear implant candidates. In this way we can gain more insight in which type of cochlear implant candidates experience moderate to severe tinnitus as well as which type of cochlear implant candidates with moderate or severe tinnitus benefit from cochlear implantation aimed at reducing their tinnitus. In this way the surgeons can do their preoperative counseling more accurately. Besides, if we gain more insight it would also be possible to select suitable patients, with single sided deafness and moderate to severe tinnitus with insufficient reaction to conservative therapies, to undergo a cochlear implantation on their functional deaf ear for tinnitus reduction.

The next step would be to do the electrical stimulation study more extensively in patients with persistent moderate or severe tinnitus after cochlear implantation. This should be a long-term study with at least 12 months follow-up. In this study, electrode stimulation for tinnitus suppression must be combined with full-electrode stimulation for speech discrimination. In every patient different electrode stimulations should be tried. Both white noise stimulation as well as tinnitus matching stimulation based on psychoacoustic methods such as sound matching, pitch matching and loudness matching should be tried. The effect of the stimulus on tinnitus should be evaluated both using a visual analogue scale (VAS) as well as by performing tinnitus handicap questionnaires. If tinnitus suppression by electrical stimulation is successful in regular cochlear implant patients, later on this kind of therapy could also be tried in patients with single sided deafness.

The last step for future research would be to redo the PET scan study in a larger study population in which patients who describe tinnitus reduction that only develops months after the implantation (plastic reorganization) are compared with patients with persistent

tinnitus after cochlear implantation and see if there are differences in brain activation between these two populations.

CONCLUSIONS

- Cochlear implantation has a positive effect on tinnitus in most of the cochlear implant candidates that had preoperative tinnitus (Chapters 2, 3 and 5).
- The tinnitus handicap is generally small after cochlear implantation. However, some patients (still) experience a serious tinnitus handicap, including feelings of anxiety and depression. These complaints require appropriate management (Chapters 2, 3 and 5).
- It is important to be able to predict the effects of cochlear implantation on tinnitus. Our study shows that particularly the negative effects are, to a certain extent, predictable. The better the pre-op situation, with regard to tinnitus handicap and hearing handicap, the more chance there is of worsening of the tinnitus afterwards. However, more research is necessary on this topic (Chapters 2 and 4).
- Masking seems to be an important mechanism in tinnitus reduction by cochlear implantation, but also cochlear implantation has an effect on general well-being (often a positive effect), which may also have consequences for the tinnitus handicap experienced after implantation (Chapters 2, 3, 6 and 7).
- Information about the effects of cochlear implantation on tinnitus should be provided to cochlear implant candidates (Chapter 8).

REFERENCES

- Akdogan, O., Ozcan, I., Ozbek, C., & Dere, H. (2009). Tinnitus after cochlear implantation. *Auris Nasus Larynx*. <https://doi.org/10.1016/j.anl.2008.04.005>
- Arts, R.A.G.J., George, E.L.J., Chenault, M.N., & Stokroos, R.J. (2015). Optimizing intracochlear electrical stimulation to suppress tinnitus. *Ear and Hearing*. <https://doi.org/10.1097/AUD.000000000000090>
- Arts, R. A. G. J., George, E. L. J., Griessner, A., Zierhofer, C., & Stokroos, R. J. (2015). Tinnitus suppression by intracochlear electrical stimulation in single-sided deafness: A prospective clinical trial - Part i. *Audiology and Neurotology*. <https://doi.org/10.1159/000381936>
- Baguley, D. M., & McFerran, D. J. (2002). Current perspectives on tinnitus. *Archives of Disease in Childhood*. <https://doi.org/10.1136/adc.86.3.141>
- Bovo, R., Ciorba, A., & Martini, A. (2011). Tinnitus and cochlear implants. *Auris Nasus Larynx*. <https://doi.org/10.1016/j.anl.2010.05.003>
- Chang, J. E., & Zeng, F. G. (2012). Tinnitus suppression by electric stimulation of the auditory nerve. *Frontiers in Systems Neuroscience*. <https://doi.org/10.3389/fnsys.2012.00019>
- Cox, R. M., & Alexander, G. C. (1995). The abbreviated profile of hearing aid benefit. *Ear and Hearing*. <https://doi.org/10.1097/00003446-199504000-00005>
- Davis, P. B., Paki, B., & Hanley, P. J. (2007). Neuromonics tinnitus treatment: Third clinical trial. *Ear and Hearing*. <https://doi.org/10.1097/AUD.0b013e3180312619>
- Festinger, L. (1961). The psychological effects of insufficient rewards. *American Psychologist*. <https://doi.org/10.1037/h0045112>
- Festinger, L. (1962). Cognitive dissonance. *Scientific American*. <https://doi.org/10.1038/scientificamerican1062-93>
- Goebel, G., & Hiller, W. (1994). [The tinnitus questionnaire. A standard instrument for grading the degree of tinnitus. Results of a multicenter study with the tinnitus questionnaire]. *HNO*.
- Henry, J. A., Zaugg, T. L., Myers, P. J., & Schechter, M. A. (2008). Using Therapeutic Sound With Progressive Audiologic Tinnitus Management. *Trends in Amplification*. <https://doi.org/10.1177/1084713808321184>
- Kleine Punte, A., De Ridder, D., & Van De Heyning, P. (2013). On the necessity of full length electrical cochlear stimulation to suppress severe tinnitus in single-sided deafness. *Hearing Research*. <https://doi.org/10.1016/j.heares.2012.08.003>
- Klooststra, F. J. J., Arnold, R., Hofman, R., & Van Dijk, P. (2015). Changes in tinnitus after cochlear implantation and its relation with psychological functioning. *Audiology and Neurotology*. <https://doi.org/10.1159/000365959>
- Klooststra, F. J. J., Verbist, J., Hofman, R., Free, R. H., Arnold, R., & Van Dijk, P. (2019). A Prospective Study of the Effect of Cochlear Implantation on Tinnitus. *Audiology and Neurotology*. <https://doi.org/10.1159/000495132>

- Kompis, M., Pelizzone, M., Dillier, N., Allum, J., Demin, N., & Senn, P. (2012). Tinnitus before and 6 months after cochlear implantation. *Audiology and Neurotology*. <https://doi.org/10.1159/000335126>
- Kuk, F. K., Tyler, R. S., Russell, D., & Jordan, H. (1990). The psychometric properties of a tinnitus handicap questionnaire. *Ear and Hearing*. <https://doi.org/10.1097/00003446-199012000-00005>
- Meikle, M. B., Henry, J. A., Griest, S. E., Stewart, B. J., Abrams, H. B., McArdle, R., ... Vernon, J. A. (2012). The tinnitus functional index: Development of a new clinical measure for chronic, intrusive tinnitus. *Ear and Hearing*. <https://doi.org/10.1097/AUD.0b013e31822f67c0>
- Newman, C. W., Jacobson, G. P., & Spitzer, J. B. (1996). Development of the tinnitus handicap inventory. *Archives of Otolaryngology - Head and Neck Surgery*. <https://doi.org/10.1001/archotol.1996.01890140029007>
- Olze, H., Szczepek, A. J., Haupt, H., Förster, U., Zirke, N., Gräbel, S., & Mazurek, B. (2011). Cochlear implantation has a positive influence on quality of life, tinnitus, and psychological comorbidity. *Laryngoscope*. <https://doi.org/10.1002/lary.22145>
- Pan, T., Tyler, R. S., Ji, H., Coelho, C., Gehringer, A. K., & Gogel, S. A. (2009). Changes in the tinnitus handicap questionnaire after cochlear implantation. *American Journal of Audiology*. [https://doi.org/10.1044/1059-0889\(2009/07-0042\)](https://doi.org/10.1044/1059-0889(2009/07-0042))
- Quaranta, N., Wagstaff, S., & Baguley, D. M. (2004). Tinnitus and cochlear implantation. *International Journal of Audiology*. <https://doi.org/10.1080/14992020400050033>
- Rubinstein, J. T., Tyler, R. S., Johnson, A., & Brown, C. J. (2003). Electrical suppression of tinnitus with high-rate pulse trains. *Otology and Neurotology*. <https://doi.org/10.1097/00129492-200305000-00021>
- Schwartz, C. E., Andresen, E. M., Nosek, M. A., & Krahn, G. L. (2007). Response Shift Theory: Important Implications for Measuring Quality of Life in People With Disability. *Archives of Physical Medicine and Rehabilitation*. <https://doi.org/10.1016/j.apmr.2006.12.032>
- Souliere, C. R., Kileny, P. R., Zwolan, T. A., & Kemink, J. L. (1992). Tinnitus Suppression Following Cochlear Implantation: A Multifactorial Investigation. *Archives of Otolaryngology--Head and Neck Surgery*. <https://doi.org/10.1001/archotol.1992.01880120017004>
- Vernon, J. (1977). Attempts to relieve tinnitus. *J Am Audiol Soc*.
- Vernon, J. A., & Meikle, M. B. (2003). Masking devices and alprazolam treatment for tinnitus. *Otolaryngologic Clinics of North America*. [https://doi.org/10.1016/S0030-6665\(02\)00163-9](https://doi.org/10.1016/S0030-6665(02)00163-9)
- Visser, M. R. M., Oort, F. J., & Sprangers, M. A. G. (2005). Methods to detect response shift in quality of life data: A convergent validity study. *Quality of Life Research*. <https://doi.org/10.1007/s11136-004-2577-x>
- Wilson, P. H., Henry, J., Bowen, M., & Haralambous, G. (1991). Tinnitus reaction questionnaire: Psychometric properties of a measure of distress associated with tinnitus. *Journal of Speech and Hearing Research*. <https://doi.org/10.1044/jshr.3401.197>

9

SUMMARY & SAMENVATTING

SUMMARY

Tinnitus is the perception of sound that occurs in the absence of external sound. The prevalence of tinnitus in the general population is between 5 and 43%; 10 to 30% of these patients suffer from tinnitus that lasts for more than five minutes at a time.

Since tinnitus is probably a result of hearing loss, this is common in cochlear implant (CI) candidates, i.e. patients with severe sensorineural hearing loss. Previous research has described a prevalence of tinnitus in cochlear implant candidates ranging from 66 to 86% and 17 to 35% of these patients reported severe tinnitus.

Many studies have shown that the suppression of tinnitus is a co-occurring effect of cochlear implantation, showing that suppression of tinnitus occurs in 15 to 95% of the cases. However, some cochlear implant patients have reported an exacerbation (1 to 10%) or even the onset (0 to 23%) of tinnitus after implantation.

This thesis aims to obtain more insight into the number of patients that might benefit from cochlear implantation in the population of patients with severe binaural sensorineural hearing loss. We tried to clarify the preoperative factors that can predict the outcome of cochlear implantation on tinnitus. We also explored single electrode stimulation strategies to reduce tinnitus perception and furthermore we tried to measure central nervous system changes associated with tinnitus reduction in cochlear implant recipients.

Chapter 1 contains a general introduction to tinnitus, the pathophysiology of subjective tinnitus and possible treatment strategies to treat tinnitus.

Chapter 2 is a review of the current knowledge concerning cochlear implantation and tinnitus. The purpose of this chapter was to give a brief overview of the research in the area of cochlear implants and tinnitus considering (1) the effect of cochlear implantation on tinnitus, (2) factors predicting successful tinnitus reduction, (3) the role of strategies for electrical stimulation and (4) neurophysiological insights gained from neuroimaging studies.

Chapter 3 describes a retrospective questionnaire study that aimed to address the prevalence of tinnitus in cochlear implant patients and the changes after cochlear implantation with respect to tinnitus, tinnitus handicap, and anxiety or depression. In this study the prevalence of tinnitus in cochlear implant patients is 51%. The tinnitus severity

is generally mild to moderate. Cochlear implantation reduces tinnitus in an important part of the patients (56%), but in a small part of the patients (28%) cochlear implantation has a negative influence on tinnitus. However, in the patients who show tinnitus deterioration the tinnitus handicap does not increase and in the patients who show tinnitus onset after implantation the tinnitus handicap is mild. The implantation has a mildly positive effect on anxiety and depression, which is most likely caused by improvement of hearing ability.

Chapter 4 describes a study, based on the retrospective questionnaire study, which aimed to create prognostic models, using binary logistic regression analyses to predict positive or negative changes in tinnitus after cochlear implantation. This study shows that the lower the preoperative tinnitus handicap and the preoperative hearing handicap, the higher the chance that cochlear implantation will worsen tinnitus. Our results might suggest that preoperative THQ and APHAB screening could be meaningful.

Chapter 5 is a continuation of the studies in chapters 3 and 4 and describes a prospective questionnaire study in 44 CI patients. The aim of this study was to determine the effects of cochlear implantation on tinnitus and to explore which factors can influence the effect of cochlear implantation on it. This study shows that cochlear implantation can help to reduce tinnitus and the tinnitus handicap in at least 28% of the patients with preoperative tinnitus. In 72% of the patients the tinnitus remained after implantation. None of the patients developed tinnitus after implantation. A shorter duration of tinnitus prior to implantation, a more fluctuating type of tinnitus, a higher tinnitus handicap prior to implantation and a round-window surgical approach might have a positive influence on the effect of cochlear implantation on tinnitus.

Chapter 6 describes a study in which we tested the simplest possible method for electrical stimulation via a cochlear implant, where just a single electrode was activated. Potentially, such a mode of stimulation could be combined with strategies in which the remaining electrodes were used for speech perception. The purpose of this study was to investigate whether single-electrode stimulation could reduce the loudness of tinnitus. The stimulation electrode, stimulation rate, and stimulation amplitude were varied, to seek for an optimal suppression method. Significantly more tinnitus reduction was observed with stimuli at a moderate intensity level compared to stimuli at near-threshold level. No significant differences in tinnitus levels resulted from the different pulse rates and stimulation sites. However, the effect of single-electrode stimulation on tinnitus is relatively insignificant in comparison to the effect of full-array stimulation, but in some individual cases sustained single electrode stimulation may be beneficial for tinnitus management.

Chapter 7 describes a study that investigated the influence of a cochlear implant on the neural activity in tinnitus-related brain areas by making labelled water (H_2^{15}O) PET scans. Two groups of patients were included in this study; one group that experienced tinnitus reduction during CI activation and one group that experienced no tinnitus reduction during CI activation. Our hypothesis was that the group of patients with tinnitus reduction during CI activation would show less activity in tinnitus related brain areas during CI activation. The scans were made before and after switching the cochlear implant on and off, to examine correspondences with the subjective tinnitus experience of the patients. With the cochlear implant on we found activation of the bilateral auditory cortices in the whole group of subjects. This activation was most prominent on the right side. The prominent activation in the right auditory cortex is consistent with the non-language content of the sound stimulus used. We found no significant brain activation or inhibition associated with tinnitus inhibition by the cochlear implant. This could be due to the small number of subjects, or because differences in brain activation are too subtle to be detected by PET-scanning.

SAMENVATTING

Tinnitus is het horen van geluid waarbij geen externe geluidsbron aan te wijzen is. De prevalentie van tinnitus in de algemene populatie ligt tussen 5 en 43%. Van deze patiënten ervaart 10-30% tinnitus voor langer dan 5 minuten per keer.

Aangezien tinnitus in het algemeen het gevolg is van gehoorverlies, komt tinnitus vaak voor bij kandidaten voor een cochleair implantaat (CI), met andere woorden bij patiënten met een ernstig perceptief gehoorverlies. Eerder onderzoek beschrijft een tinnitus-prevalentie in de populatie van CI-kandidaten van 66-86% en 17-35% van deze patiënten rapporteren ernstige tinnitus.

Veel onderzoeken laten zien dat reductie van tinnitus vaak voorkomt als een bijkomend effect van cochleaire implantatie, wat primair gericht is op verbetering van het gehoor. Reductie van tinnitus na cochleaire implantatie komt voor in 15 tot 95% van de gevallen. Echter, bij sommige CI-patiënten verergert de tinnitus postoperatief (1 tot 10%) of ontstaat er tinnitus postoperatief (0-23%).

Dit proefschrift heeft als doel meer inzicht te verkrijgen in het aantal patiënten met een ernstig bilateraal perceptief gehoorverlies en tinnitus dat baat kan hebben bij cochleaire implantatie. We hebben onderzocht welke preoperatieve factoren het effect van cochleaire implantatie op tinnitus kunnen voorspellen. We hebben verschillende eenkanaals stimulatie strategieën geëxploreerd om tinnitus te onderdrukken. Bovendien hebben we bij CI-patiënten hersenactiviteit gemeten die mogelijk geassocieerd is met tinnitus.

Hoofdstuk 1 bevat een algemene introductie over tinnitus, de pathofysiologie van tinnitus en de mogelijke behandelstrategieën aangaande tinnitus.

Hoofdstuk 2 is een review van de huidige kennis omtrent cochleaire implantatie en tinnitus. Het doel van dit hoofdstuk is een overzicht te geven van de studies die reeds verricht zijn naar (1) het effect van cochleaire implantatie op tinnitus, (2) factoren die reductie van tinnitus na een cochleaire implantatie kunnen voorspellen, en (3) de rol van verschillende typen elektrische stimulatie aangaande tinnitus reductie. Dit hoofdstuk geeft ook een overzicht van neurofysiologische inzichten die tot nu toe verkregen zijn uit 'neuro-imaging' onderzoeken bij CI-patiënten.

Hoofdstuk 3 beschrijft een retrospectief vragenlijst onderzoek dat als doel heeft de prevalentie van tinnitus in CI-patiënten in kaart te brengen en tevens het effect van cochleaire implantatie op tinnitus, tinnitus handicap, angst en depressie te onderzoeken. De prevalentie van tinnitus in de populatie van CI-kandidaten in dit onderzoek was 51%. De ernst van de tinnitus was over het algemeen mild tot matig. Het grootste deel van de patiënten (56%) ervoer tinnitus reductie na de implantatie, maar in een klein gedeelte (28%) van de patiënten had de implantatie een negatief effect op tinnitus. Echter, bij de patiënten die een verergering van hun tinnitus ervoeren na de implantatie werd de tinnitus handicap niet groter en bij de patiënten waarbij tinnitus ontstond na de implantatie was de tinnitus handicap over het algemeen mild. Een cochleaire implantatie heeft een licht positief effect op gevoelens van angst en depressie. Dit positieve effect komt waarschijnlijk voort uit de verbetering van het gehoor na de implantatie.

Hoofdstuk 4 beschrijft een studie die gebaseerd is op het retrospectieve vragenlijst onderzoek. In deze studie hebben we prognostische modellen ontwikkeld die een positief of negatief effect van cochleaire implantatie op tinnitus kunnen voorspellen. Dit hebben we gedaan door gebruik te maken van binaire logistische regressie-analyses. Deze studie laat zien dat hoe lager de preoperatieve tinnitus- en gehoorhandicap zijn, hoe groter de kans is dat een cochleaire implantatie tinnitus verergert. Onze resultaten suggereren dat preoperatieve screening middels vragenlijsten, zoals de THQ en APHAB, zinvol kan zijn.

Hoofdstuk 5 is een vervolg op de onderzoeken van hoofdstuk 3 en 4 en beschrijft een prospectief vragenlijst onderzoek onder 44 CI-patiënten. Het doel van dit onderzoek was te bepalen wat het effect is van cochleaire implantatie op tinnitus en te exploreren welke factoren het effect van cochleaire implantatie op tinnitus kunnen beïnvloeden. Dit onderzoek laat zien dat cochleaire implantatie, reductie van tinnitus en tinnitus handicap kan bewerkstelligen in ten minste 28% van de patiënten met preoperatieve tinnitus. In 72% van de patiënten was er na de implantatie nog steeds tinnitus aanwezig. Geen van de patiënten ontwikkelde tinnitus na de implantatie. Een kortere duur van de tinnitus preoperatief, een meer fluctuerend type tinnitus, een hogere preoperatieve tinnitus handicap en een ronde venster benadering tijdens chirurgie hadden een positieve invloed op het effect van cochleaire implantatie op tinnitus.

Hoofdstuk 6 beschrijft een studie om de meest simpele vorm van elektrische stimulatie via een CI te onderzoeken, namelijk stimulatie via slechts 1 elektrode van het implantaat. Mogelijk kan deze vorm van stimulatie gecombineerd worden met stimulatie strategieën waarbij de overige elektroden gebruikt worden voor spraakherkenning. Het doel van

deze studie was te onderzoeken of stimulatie van een enkele elektrode de luidheid van tinnitus kan reduceren. De plaats van de gestimuleerde elektrode, de snelheid van de stimulus en de amplitude van de stimulus werden tijdens dit onderzoek gevarieerd om zo de beste vorm van stimulatie voor tinnitus reductie te vinden. Significanter meer tinnitus reductie werd gevonden bij stimulatie met een matige luidheid van de stimulus wanneer we deze vergeleken met stimuli die net hoorbaar waren voor de patiënt. We vonden geen significante verschillen in mate van tinnitus reductie tussen stimulatie met verschillende stimulatie snelheden en stimulatie op verschillende elektrodes. Het effect van stimulatie van een enkele elektrode op tinnitus is relatief insignificant vergeleken met het effect van stimulatie van de gehele elektrode, maar bij sommige individuele patiënten kan langdurige stimulatie van een enkele elektrode mogelijk een bijdrage leveren aan de behandeling van tinnitus.

Hoofdstuk 7 beschrijft een studie die de invloed van een cochleair implantaat op neurale activiteit in tinnitus gerelateerde hersengebieden onderzoekt middels het maken van PET-scans met gelabeld water ($H_2^{15}O$). In dit onderzoek hebben we twee groepen vergeleken: een groep waarbij het CI de tinnitus onderdrukt tijdens activatie van het CI en een groep waarbij het CI dat niet doet. Onze hypothese was dat de groep met onderdrukking van de tinnitus bij activatie het CI, minder hersenactiviteit zou vertonen in tinnitus gerelateerde hersengebieden wanneer het CI aanstond. De scans werden gemaakt voor en na het uitzetten van het CI en er werd gekeken of de mate van activiteit in de hersenen overeenkwam met de subjectieve tinnitus beleving van de patiënten. Wanneer het CI aanstond vonden we activatie in de bilaterale auditieve cortices in de gehele groep van patiënten. Deze activatie was het meest prominent aan de rechterzijde. De prominente activatie in de rechter auditieve cortex is consistent met de niet-talige stimulus die aangeboden werd wanneer het CI aanstond. We vonden geen significante hersenactivatie of -inhibitie gerelateerd aan tinnitus inhibitie door het CI. De verklaring hiervoor kan zijn dat we een te klein aantal patiënten gescand hebben of dat de verschillen in hersenactiviteit te subtiel zijn om te meten met een PET-scan.

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CURRICULUM VITAE

Francka Jansje Joucka Kloostra werd op 3 februari 1985 geboren in Groningen als dochter van Reinder en Alie. Ze groeide op in Roden en op het R.S.G. de Borgen te Leek behaalde ze in 2003 haar atheneum diploma.

In september 2003 begon zij haar studie Geneeskunde aan de Rijksuniversiteit Groningen. In 2004 behaalde zij haar propedeuse. Tijdens haar studie participeerde zij bij onderzoek naar de functie van endotheliale progenitor cellen bij niertransplantatie patiënten op de afdeling Nefrologie in het Universitair Medisch Centrum Groningen. Francka heeft haar co-schappen in het Universitair Medisch Centrum Groningen en het Tjongerschans te Heerenveen gelopen. De senior co-schappen radiologie en Keel-, Neus-, en Oorheelkunde en hoofd-halschirurgie heeft zij in het Universitair Medisch Centrum Groningen gedaan. Haar afstudeerscriptie deed ze ook bij de afdeling Keel-, Neus-, en Oorheelkunde en hoofd-halschirurgie in het Universitair Medisch Centrum Groningen naar radiologische bevindingen bij het CHARGE-syndroom met betrekking tot gehoor- en voedingsproblematiek. Hieruit volgde in samenwerking met het Radboud Universitair Medisch Centrum Nijmegen in 2016 een publicatie.

Na het behalen van haar artsexamen in 2009 is Francka gestart met de opleiding Keel-, Neus- en Oorheelkunde en hoofd-halschirurgie in het Universitair Medisch Centrum Groningen waarin zij dit promotie onderzoek combineerde met de opleiding tot KNO-arts. Haar perifere stages deed zij in het Martini Ziekenhuis Groningen. Naast haar promotie onderzoek publiceerde zij tijdens haar opleiding een tweetal case reports in het Nederlands Tijdschrift voor KNO-heelkunde. Het eerste case report ging over plotseling perceptief gehoorverlies bij patiënten met het CREST syndroom, en het tweede case report over verplaatsing van de cornu superius van het thyroid als verklaring van globus of slikklachten. In mei 2017 rondde ze haar opleiding tot KNO-arts af.

Vanaf juli 2017 is zij werkzaam als KNO-arts in het Ommelanders Ziekenhuis Groningen.

Francka heeft relatie met Rutger Kussendrager. Zij hebben samen 2 kinderen: Steyn en Annefien.

PUBLICATIES

Sudden deafness bij patiënt met CREST-syndroom

Kloostra FJJ, van der Laan BFAM, van der Beek JMH. Nederlands Tijdschrift voor Keel-Neus-Oorheelkunde, 2014, 20e jaargang, nr. 1

Verplaatsing van het cornu superius van het thyroïd als verklaring voor globus of slikklachten

Kloostra FJJ, Dikkers FG. Nederlands Tijdschrift voor Keel-Neus-Oorheelkunde, 2015, 21e jaargang, nr. 2

Changes in tinnitus after cochlear implantation and its relation with psychological functioning.

Kloostra FJJ, Arnold R, Hofman R, Van Dijk P. Audiol Neurotol. 2015;20(2):81-9. doi: 10.1159/000365959. Epub 2014 Dec 18.

Cochlear Implants & Tinnitus

Kloostra FJJ, Arnold R, van Dijk P. Tinnitus, Clinical and Research Perspectives, Plural Publishing, 2016, Chapter 13, p. 213-226.

CT findings of the temporal bone in CHARGE syndrome: aspects of importance in cochlear implant surgery.

Vesseur AC, Verbist BM, Westerlaan HE, **Kloostra FJJ**, Admiraal RJC, van Ravenswaaij-Arts CMA, Free RH, Mylanus EAM. Eur Arch Otorhinolaryngol. 2016 Dec;273(12):4225-4240. doi: 10.1007/s00405-016-4141-z. Epub 2016 Jun 20.

Models to predict positive and negative effects of cochlear implantation on tinnitus.

Kloostra FJJ, Arnold R, Hofman R, Burgerhof JGM, van Dijk P. Laryngoscope Investig Otolaryngol. 2018 Dec 14;4(1):138-142. doi: 10.1002/lio2.224. eCollection 2019 Feb.

A Prospective Study of the Effect of Cochlear Implantation on Tinnitus.

Kloostra FJJ, Verbist J, Hofman R, Free RH, Arnold R, van Dijk P. Audiol Neurotol. 2018;23(6):356-363. doi: 10.1159/000495132. Epub 2019 Feb 8.

Changes in Tinnitus by Cochlear Implantation: A Parametric Study of the Effect of Single-Electrode Stimulation.

Kloostra FJJ, de Kleine E, Free RH, Hofman R, Van Dijk P. Audiol Neurotol. 2020 Sep 7:1-9. doi: 10.1159/000509202. Online ahead of print.