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The role of transcutaneous Vagus Nerve Stimulation (t-VNS) paired with tones in the treatment of Tinnitus through the manipulation of neural plasticity

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Recerca Neurociència Cognitiva i Tecnologies de la información
PRACTICUM I
Teacher: Toni Valero Cabré

Irene Calduch Ortega
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1. ABSTRACT

The tinnitus is a sound perception defined as the psychosensory phenomenon experienced in the auditory cortex and different mechanisms can produce it. The tinnitus can be subjective or objective, which means they can be felt as own in the absence of an exterior stimulation and non-observed by other than the patient or they could be produced by external sources. As it is known, there are different physiopathological theories to explain this phenomenon but we believe that none of them can explain with accuracy the complexity of tinnitus. Hence the project is focus on the demonstration of the changes that the combination of the transcutaneal stimulation of the Vague Nerve (t-VNS) paired with tones can produce in the plasticity of the auditory cortex. Additionally, we will test the effectiveness of the t-VNS paired with tones compared with a single therapy of t-VNS or tones to treat chronic tinnitus as it is shown in animal, particularly rodent, literature that provides perfect and inspiring test bench. We will do the test in three randomized groups of 15 people and hence a total sample of 45 individuals. These individuals have to have a subjective chronic tinnitus derived from exposed-noise hearing loss. One group will receive a therapy of the tVNS combined with tone while the other two groups will receive a single treatment therapy with just tVNS or just tones. The idea is to do a pre-treatment and post-treatment resting state functional magnetic resonance imaging (fMRI) to detect the changes in functional connectivity at rest. Also, to do a comparison between the fMRI of the different groups along with a pre-treatment and post-treatment application of a Tinnitus Questionnaire (TQ) and a Tinnitus Handicap Questionnaire (THQ) to study the improvement of the subjective complaints of the tinnitus.

2. ABSTRACT FOR NON-SPECIALIZED PUBLIC

Tinnitus is a sound perception defined as a psychological sensorial phenomenon which means that who suffers it hears a continued white noise or high pitch noise, permanently or in specific moments. That noise can be subjective: it means there is not any external stimulation. Meanwhile, if it is objective means that there is an external source which produces it. There are many theories that try to explain why and how this phenomenon is produced but we believe, because of the complexity of tinnitus, that it is impossible. The objective of this study is to assess the theory of the auditory system implication, to do that; we will apply an experiment already done in rodents to humans. The experiment will be done in three different groups of people. One will receive a combined therapy of two techniques while the other two will receive a single therapy. The first group will receive a stimulation of the vague nerve through the cavum of the ear while pairing it with a series of tones. Before and after that we will do a functional magnetic resonance imaging (fMRI) in a resting stat so we can see if the combination of these two techniques produces any change in the connectivity of the brain at rest. The group two will receive a single technique therapy of the stimulation of the vague nerve while the third group will receive a single technique therapy of tones. We will also do a pre-treatment and post-treatment fMRI to these groups to compare with the first group. It will be important to also do some pre-treatment and post-treatment questionnaires to study the subjective complaints of the tinnitus.

3. CONTEXT, CONCEPTUAL FRAMEWORK AND STATE OF KNOWLEDGE

3.1. What is tinnitus?

As it is explained in the seminar published by the Cambridge University and the Hospitals NHS Foundation about tinnitus (Baguley, D., McFerran, D., & Hall, D., 2013), it is a psychosensory phenomenon that occurs in the auditory system that can be subjective or objective depending if the experience comes from the patient itself or if the observer can hear it too. Tinnitus itself is a medical symptom and not a disease or illness and the risk factors to suffer it are hearing loss, ototoxic medication, head injury and depression. Normally, the sensation is a hissing, sizzgling or ringing sound but there exist more complex sounds such as music or voices, which are indistinct and without meaning compared with the ones that occur with psychotic illness

3.2. Epidemiology

It is known that between a 10% to a 17% of the total population suffer from tinnitus and that it exist a total of 85% of comorbidity between hearing diseases and tinnitus (Clínica Universidad de Navarra, cited in Cinfasalud, 2018). No t only that but the prevalence of tinnitus increases with age to 70 years and the prevalence between men and women is similar, with more difficult to know the prevalence in children since they seem less likely to be distressed by the perception (Davis, A., & El Rafaie, A., 2000 cited in Baguley, D., McFerran, D., & Hall, D., 2013). About incidence and longitudinal studies there isn't much information.

The risk factor known for developing tinnitus and the condicionts associated with the tinnitus symptoms (Baguley, D., McFerran, D., & Hall, D., 2013) are ontological infections, neoplastic problems, labyrinthine problems and others, also neurological, traumatic, orofacial, cardiovascular, rheumatological, immune-mediated, endocrine, metabolic, psychological and ototoxic problems (Table 1).

3.3. Pathophysiological mechanism

<u>Cochlear models</u>

1. Theory of Spontaneous Otoacoustic Emissions (SOE) (Gold, T., 1948 & Kemp, 1979): it was thought that the tinnitus was a result of the contractile spontaneous activity of the cilia from the external ciliated cells and that it was possible to mesure them objectively. It was postulated but not assessed that the aspirin could block those spontaneous emissions.
2. Theory of Decoupling linked to Traumatism (Tondero, 1980 cited in Curet, C., & Roitman, D., 2016): it postulates that the external ciliated cells from the Corti organ should normally have contac with the tectorial membrane in the presence of sound. If for some reason these two decoupling, it appears in the absence of sound an abnormal bio-electrical activity that is perceived as a buzz.
3. Theory of the Discordant Damages between the external and internal ciliated cells (Curet, C., & Roitman, D., 2016): it again talks about the external ciliated cells, which through the Medial Efferent System exert an inhibiting control above the activity of the internal ciliated cells. When this mechanism fails because of some injury the activity from the internal ciliated cells raises and provokes a change in the perception of the background noise.
4. Biochemical Origin in the Generation of Tinnitus against Stress (Sahley, et al., 2013): it postulates that the mechanism is based on the endogenous dynorphin neuromodulators that can be found in the presynaptic level on the axons in the lateral efferent beam of the olive-cochlear. This beam does a synapse with the cochlear auditory efferent dendrites type-I of the external cochlear cells. It is possible that because of the synaptic stress linked through the *Locus Coeruleus* of the protuberance a dinorfine presynaptic liberation is induced and hence an stimulation that enhance the inhibitory effects of the gluatamate neurotransmitter in the NMDA receptor. The result is a neural tinnitus in the auditory fiber.

<u>No Cochlear Models</u>

1. Neurophysiological Model by Jastreboff-Hazell (Curet, C., & Roitman, D., 2016): **One of the most accepted theories nowadays.** Studied also by Dauman, it says that independently from the origin of the tinnitus there is a component in all of the responsible for the adaptation. This adaptation depends on the interaction of some areas of the CNS. The tinnitus is detected in the

brainstem and in the mesenfalic subcortical auditory center on the medium geniculated body. It is made conscious in the temporal auditory cortex.

2. Increase of the neural activity (Evans, Eggermon, J. J.; Tyler, R., n.d., cited in Curet, C., & Roitman, D., 2016): Some experiments with animals suggest an increase of the neural activity.
3. Theory of the synchronization of the neural discharges (Eggermont, J. J., Salvi R. J., n.d., cited in Curet, C., & Roitman, D., 2016): The demyelinated auditory fibers can discharge synchronously without an external sound stimulation producing tinnitus.
4. Chronic pain analogy (Moller, A. R., n.d., cited in Curet, C., & Roitman, D., 2016): It seems that chronic pain an tinnitus could be produce by similar mechanisms.
5. Phantom limb pain analogy (Goodhill, 1950): The deprivation of an specific cochlear area can reduce the cortical activity linked to an specific auditory frequency in a short-term basis.
6. Theory of the influence of the prefrontal cortex (Curet, C., & Roitman, D., 2016): The prefrontal cortex have a role in the synthesis of the information from the exterior and could modulate the intensity of the tinnitus.
7. Theory of the dysrhythmia thalamus-corticla (Curet, C., & Roitman, D., 2016): An electrical dysrhythimia at this level coul be treated by drugs or surgery and could explain chronic pain, limb pain, depression and others.
8. Theory of the dysfunction of the medial efferent via (Eggermon, J. J., 2004; Hazell, Jastreboff, 1993): This via would have an inhibitory function in the perception of the sound and the tinnitus.
9. Theory of the somatic modulation of the tinnitus (Levine, R. A., 2006): Some people can modify their tinnitus through corporal movements which makes deduce that there is a link between the auditory via and the somatic sensorial via.
10. Aberrant activity (Curet, C., & Roitman, D., 2016): Also **one of the most accepted theories nowadays**. This theory considers that the tinnitus is the result of the abnormal activity of the epileptiform discharges produced in some areas of the auditory system from the cochlea to the brain cortex. This abnormal activity is process in an unsual way which leads to a misinterpretation of it as a noise.

3.4. Treatments

A. Sound Treatments
It implies the use of external noises to alter the perception of the patient and their reaction to the tinnitus and it can be done by masking the tinnitus, enrichment of the ambient sound, hearing aids, music devices or the Tinnitus Retraining Therapy (Curet, C., & Roitman, D., 2016).

B. Psychological Treatments
Behavioral therapy (Curet, C., & Roitman, D., 2016) is based on the emotional reaction of the patient to the tinnitus, so the idea is to change that reaction through Cognitive-Behavioral Therapy, Mindfulness, Acceptation and Compromise Therapy, Tinnitus Activities Treatment and Progressive Tinnitus Therapy.

C. Pharmacological Treatments
There is no single pharmacological treatment hence it has to be used along with other treatment mechanisms and personalized for each individual with tinnitus. Some of the drugs used for the treatments are: anesthetics, antagonists of the glutaminergic receptors, antiepileptics, antidepressives, dopaminérgica antagonists, antihistaminics and other drugs.

D. Physical Treatments
This includes hyperbaric oxygenation, Transcraneal Stimulation with direct electric current, Magnetic Trasncraneal Stimulation, Deep Cerebral Stimulation, Stimulation with superficial brain implants and Stimulation of the Vague Nerve.

E. Surgery Treatments
There is a little role of the surgery in tinnitus cases but it includes cochlear implants.

3.5. Conceptual Framework

As it has been said, VNS is one of the physical treatments used for tinnitus. In fact, it has been demonstrated that tVNS alone is feasible yet not with clinically significant results in tinnitus complaints improvements (Keuzer, P., Landgrebe, M., Resch, M., et al., 2014). Hence, it is important to clarify that it is safe to use this technique in patients without any kind of cardiac problem history.

Few investigations have proven that VNS paired with tones can be also feasible and safe and seem to exert a beneficial effect in patients that do not take any medication (De Ridder, D., Vanneste, S., Engineer, N., et al., 2014). There is also prove that tVNS combined with sound therapy seems to improve the mood and decrease tinnitus handicaps scores along with reducing tinnitus severity (Lethimäki, J., Hyvärinen, P., Ylikoski, M., et al., 2013).

In conclusion, we will combine tVNS, proven to be safe and feasible, with tones to demonstrate that these two combine techniques can produce benefits to tinnitus patients without having to use transcraneal implants which are expensive and invasive.

4. GENERAL LONG AND SHORT-TERM OBJECTIVES

The general long-term goal of the project is to generate efficient and longer lasting treatments for tinnitus. It has been demonstrated that it is feasible to use Transcutaneal Vague Nerve Stimulation (tVNS) over a period of 6 months in patients with Tinnitus but there were no clinically relevant improvements of tinnitus complaints (Kreuzer, P., et al., 2014). The prospects in single tinnitus treatment is clearly weak in results to efficient and long lasting changes in the symptom therefore the idea is to change that and give tinnitus patients new ways to improve their quality live and even reverse the tinnitus symptom. Also, we will create a smart device to treat Chronic Tinnitus patients in a more personalized way; the idea is to create an easy way of treating themselves from home.

The short term goal of this project is to study the therapeutic effects of the tVNS and its role paired with tones in the plasticity of the auditory cortex. As it has been demonstrated in rats (Engineer, et al., 2011) the action of repeatedly pairing tones with tVNS is sufficient to generate specific long-lasting changes in cortical fields. As so, a series of 10 cases of Tinnitus treatment with VNS and tones pairing were studied with clinically significant improvements (De Ridder, D., et al., 2013). Hence paralleling these observations we aim to transpose this evidence obtained in rodents to human tinnitus patients and demonstrate the success of these techniques for the rehabilitation of chronic tinnitus disease, as to achieve the evidence that these two combined techniques are better that single treatment for tinnitus.

5. SPECIFIC OBJECTIVES

In order to implement our short-term goal, we have defined the following objectives:

Aim 1: We will asses compared to isolate interventions the clinical impact of combined tones and tVNS in chronic tinnitus patients with sound-exposed hearing loss and without a cardiac problem history. We will recruit 45 individuals with different tinnitus severity and we will distribute them randomly in three groups of 15 people. The first group will receive a therapy of single tVNS, the second group will receive a therapy of single tones and, finally, the third group will receive a therapy of combined tVNS paired with tones.
We will test the individuals' gap impairment and then choose the tones randomly from the interval that span the person hearing range for each individual since previous studies suggest it would reduce the cortical response, increase frequency selectivity and decrease cortical

synchronization (Eggermont, J. J. & Roberts, L. E., Kilgard, et al., cited in Engineer, et al., 2011).
For the t-VNS we will use a transcutaneous electrical nerve stimulation (TENS) device (Tens Digital 7000: 2 Outputs and 5 modes of TENS, fisaude sl., Europe). The stimulation conditions will be the following: pulse width, 200us; frequency, 30Hz; stimulation site; the cavum inferiorly in the ear (Won, S. C., Su, J. K., Dong, S. C. & Ho, Y., L., 2018). Intensity will be chose by increasing 1mA every 5s until the maximum intensity the patient will be able to tolerate.
We will perform the tVNS paired with tones 30s followed by a break of 180s for 6 h every day (Kreuzer, P. M., et al., 2014).
To assess the impact of the combined intervention we will apply a pre-treatment and post-treatment THQ and TQ in each individual to study the improvements in the subjective sensations between the different groups.
Our hypothesis is that we will find more improvements in THQ and TQ results in the group of combined therapies than in the single treatment groups.

Aim 2: We will demonstrate that tVNS paired with tones produces plasticity changes in the auditory system. For that, we will perform an fMRI for each individual of the three different groups to do a comparison between the pre-treatment and post-treatment changes in functional connectivity at rest and also to compare these changes between groups.
Our hypothesis is that we will observe clinically significant changes in pre and post treatment fMRI in all of the participants of the tVNS paired with tones group, changes that will not be found in the two other single treatment groups.

Aim 3: We will design a smart device to control the delivery of several combinations of tVNS and tones. The device will allow the patient to test himself his hearing range for then the program to choose randomly different tones from the hearing span of the individual. The device will also allow the person to test the intensity of the tVNS. The headphones will not just deliver the tone but will have a little patch to deliver stimulation in the cavum inferior.
Our hypothesis is that we will be able to treat tinnitus in an easier way with a simple device that will be able to test hearing ranges, randomly choose some frequencies from the hearing range of the patient, allow the patients to choose the tVNS intensity and discharge the stimulation pulses along with the tones.

6. MATERIAL AND METHODS: GENERAL ASPECTS

6.1. Study design and subjects

This experimental study will be an ongoing longitudinal treatment study in a three years period. The sample will be of 45 individuals diagnosed with different severity tinnitus produced by hearing loss. First of all, the patients will be distributed randomly in three groups of 15 individuals. First group will receive a combined therapy of tVNS paired with tones. Second group will be subjected to a single technique treatment of tVNS while the third will be submitted to a single technique treatment of tones. The first and third group will do a pre-treatment test of hearing range. Also, the first and second group will do a pre-treatment cardiac general test to asses that there is no cardiac problems. We will do an fMRI to all individuals of the three groups along with the questionnaires TQ and THQ to do a following pre and post treatment individual and intergroup comparison of the severity and complaints improvement depending on the treatment received.

All patients will give their written informed consent prior to inclusion together with a written confirmation that they do not have a cardiac problem history.

6.2. Materials

The material used in the study will be the following: Tinnitus Questionnaire, Tinnitus Handicap Questionnaire, a transcutaneal vagus nerve stimulation device (described in specific aim 1), mp3 players for tones administration, rs-fMRI machine (described in specific aim 2) and computers with the installation of the SPSS program for study data's analysis. Also, it will be needed the correspondent IDEs to program the device, the firmware will be programmed in C while the high level API will be programmed in python.

6.3. Methods and tasks

First there will be a meeting with the professionals who will carry out the study and then the patients' recruiting will proceed. The total sample will be obtained first and then it will be divided into three groups with a randomized method. Afterwards, the administrations of tests, the cardiac general test and the realization of the rs-fMRI will be carried out to asses that all individuals are able to submit the treatments and to obtain the pre-treatment data. After the treatment, all patients will be evaluated again through the tests and rs-fMRI along with the cardiac general test to obtain the post-treatment data together with any information about the cardiac state of the patients. After three and six months post-treatment the tests and the fMRI will be done again to evaluate if the results are consistent in time after the treatment.

Finally, we will develop a smart device able to test hearing ranges and to choose some randomized frequencies from that hearing range along with the capacity of discharge pulses to the cavum while pairing it with the chosen tones.

6.4. Inclusion and exclusion criteria

The inclusion criteria will be clinical diagnosis of tinnitus derived from a, sound-exposed hearing loss; age between 18 and 50 years.

The exclusion criteria will be patients suffering from cardiac diseases, so it does not cause any secondary effect from the tVNS; patients suffering from other auditory problems; patients with other cognitive deficits; patients in pharmacological treatments or a history of alcohol or other drugs abuse; patients with other neurological or psychiatric disorder; patients who obtain a score <15 in the MMSE (mini mental status exam, Folstein, Folsein and Mchugh, 1975), so they understand what they are going through and to be able to follow all the instructions; and patients with cognitive or attention deficits, serious brain injury, medical contraindication to receive non-invasive brain stimulation.

6.5. Statistical Analysis

For the analysis of the obtained data we will use the IBM SPSS Statistics 25 program and for analyzing the images obtained by rs-fMRI, the Brain Connectivity Toolbox.

7. MATERIALS AND METHODS DETAILED FOR SPECIFIC OBJECTIVES

A. **Aim 1:** We will asses compared to isolate interventions the clinical impact of combined tones and tVNS in chronic tinnitus patients with sound-exposed hearing loss.

The complete sample of 45 individuals will be randomly divided into three groups of 15 patients each. The first group will be subject to a single technique treatment of tVNS, the second group will receive a single technique treatment of tones and the third group will receive a combined technique of tVNS paired with tones. All 45 individuals of the sample will be submitted to a resting state fMRI. This resting state fMRI will be used to compare the areas of the brain that are activated.

The analysis of the imaging, the activated auditory areas along with other brain areas will be evaluated by the Brain Connectivity Toolbox program.
This test will be done four times, one pre-treatment time before starting any type of hearing range tests and further treatments, and three post-treatment times: one fMRI just after the treatment is finished, one 3 months after the end of the treatment and the last one 6 months after the end of the treatment.
The rs-fMRI will be performed along with THQ and TQ in all the individuals. Hence, the brain areas activated in the three samples will be compared and analyzed together with the tinnitus severity and complaints not just between groups but between pre and post treatment single group results.
THQ and TQ will give us information about any changes in the subjective experience of tinnitus in patients while rs-fMRI will be used to observe possible changes and maintenance of these changes in the neural plasticity of the brain between the different groups.
The tVNS device that will be use is Tens Digital 7000: 2 Outputs and 5 modes of TENS (fisaude sl., Europe).

<u>Expectations:</u> We hope to find clinically significant differences between the three samples. We expect group 3 (tVNS paired with tones) to develop changes in the neural plasticity of the auditory cortex and its neural connections in rest state while no changes or no clinically significant changes in group 1 (tVNS alone) and group 2 (tones alone). Same with the THQ and TQ results, were we expect to find better improvements in the subject experience and tinnitus complaints in group 3 in comparison with group 1 and 2 along with better maintenance of the improvements in time.

B. **Aim 2:** We will demonstrate that tVNS paired with tones produces plasticity changes in the auditory system.
For that we will use the rs-fMRI described in materials and methods of aim 1.
The rs-fMRI will be used to observe possible changes and maintenance of these changes in the neural plasticity of the brain of the individuals in group 3 if they are achieved.

<u>Expectations:</u> We expect to find, as described in aim 1, clinically significant changes in the neural plasticity in group 3, specifically in the auditory cortex area.

C. **Aim 3:** We will design a smart device to control the delivery of several combinations of tVNS and tones.
For that we will use the proper IDEs. The firmware will be programmed in C along with python for the programming of the high level API.
We will test it in a small sample of 15 individuals. These 15 patients will we choose with the same criteria as the ones described in aim 1.
Rs-fMRI and TQ and THQ will be executed in the patient to test the severity and complaints of the tinnitus along with the neural plasticity changes. Those will also be compared with the previous study.

<u>Expectations:</u> We expect to develop a smart device which will test the hearing range of the patient. Also, it will be able to randomly choose some different tones span the specific hearing range to deliver the tones together with the stimulation pulses. The patient will also be able to manipulate the intensity of the pulses through the device.

8. POSSIBLE PROJECT DIFFICULTIES AND COMPLICATIONS

One of the main complications that can occur is the tVNS to suppose secondary effects in the patients such as dizziness, cardiac problems or headaches along with otalgia or dermatological effects at the stimulation area.

Another breakthrough that we can find is no significant changes in the plasticity of the auditory areas or any improvement in the tinnitus complaints of the combined techniques (tVNS paired with tones) group. It could mean that there is no clinical future for these techniques and hence we will not have the opportunity to design the smart device.

Last but not least, we could find trouble in the design of the smart device or in the feasibility of it.

9. SCHEDULE DISTRIBUTION OF PHASES AND TARGETS FOR SPECIFIC OBJECTIVES

See Table 2 at section Annex

10.SCIENTIFIC, CLINICAL, SOCIAL AND TECHNOLOGICAL POTENTIAL IMPACT OF THE PROPOSAL

Scientifically and clinically, this study can asses a new approach to the treatment of any symptom or disorder through target plasticity. Not only this but will asses and give force to the belief of the neural implications of the auditory system in tinnitus.

The social potential of this study is the improvement in the quality life that it can offer to tinnitus patients apart of a new prospect for them as so in the moment there is no actual long-lasting treatment for the symptom. Furthermore, it would help economically to the patients.

Finally, in the technological field, it could make an approach to new medical instruments to treat disorders and other illnesses. It could open up a new way of tinnitus treatment, technically talking, were there would be less necessity of hospitals and expensive devices.

11. JUSTIFICATION OF THE TEAM OF RESEARCHERS, INSTITUTIONS INVOLVED, BUDGET LINE AND JUSTIFICATION

Equipment:

The neuroimaging equipment aviable at UOC’s Cognitive Neurolab facilities on a pay-per-use and pay-per-analyze basis.
Estimated RMI cost: 24.000 €

Tens device for the tVNs. We decided to use Tens Digital 7000: 2 Outputs and 5 modes of TENS (fisaude sl., Europe).
Estimated TENS devices cost: 3.090€

Team of researchers:

Two post-doctoral psychology researchers with experience in MRI and data analysis.
Two master students will be required from a neuropsychology master to be assistants.

Two post-doctoral informatics engineering researchers with experience in C and Python programming and in medical devices programming.

Two master students will be required from a informatics system and software engineering master to be assistants.
Estimated Team Researcher’s cost: 360.000 €

ESTIMATED FINAL BUDGET (equipment + staff): 387.090€ for 36 months / 3 years.

12. ISSUES OR ETHICAL IMPLICATIONS OF THE PROJECT

Although our study is focused on new methods for tinnitus treatment partients, the methods have already been assessed as safe and feasible by a case series (De Ridder, D., Vanneste, S., Engineer, N., et al., 2014). Another experiment were tVNS was the main object of study demonstrated that the use of this technique in humans have no side effects or danger repercussion.

The procedure of rs-fRMI is well regulated and has been proven safe in Tinnitus patients.

The patients will be well informed during all the process along with having the right to stop the treatment at any time once they inform us the reasons. Not only that but the importance of the objective outweighs by far the risks and burdens to the sample, as stated before (point 8, possible project difficulties and complications).

The researched will be done according to the declaration of Helsinky (1990).

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14. ANNEX

Table 1.

Typology of disease	**Specific disease**
Otological, infectious	Otitis media, labyrinthitis, mastoiditis
Otological, neoplastic	Vestibular schwannoma, meniningioma
Otological, labyrinthine	Sensorineural hearing loss, Ménière's Disease, vestibular vertigo
Otological, other	Impacted cerumen, otosclerosis, presbyacusis, noise exposure
Neurological	Meningitis, migraine, multiple sclerosis, epilepsy
Traumatic	Head or necj injury, loss of consciousness
Orofacial	Temporomandibular joint disorder
Cardiovascular	Hypertension
Rheumatological	Rheumatoid arthritis
Immune-mediated	Systemic lupus erythematosus, systemic sclerosis
Endocrine and metabolic	Diabetes mellitus, hyperinsulinaemia, hypothyroidism, hormonal changes during pregnancy
Psychological	Anxiety, depression, emotional trauma
Ototoxic medications	Analgesics, antibiotics, antineoplastic drugs, corticosteroids, diuretics, immunosuppressive drugs, non-steroidal anti-inflammatory drugs, steroidal anti-inflammatory drugs (Cianfrone, G., Pentangelo, D., Cianfrone, F., et al., 2011

	cited in Baguley, D., McFerran, D., & Hall, D., 2013)

Table 2. Schedule Distribution of Phases

	Year 1												**Year 2**												**Year 3**											
Months	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Meeting with professionals	■																																			
Recruitment of the sample		■																																		
AIM 1																																				
Pre-treatment tests and rs-fMRI			■																																	
Treatments				■	■	■	■	■	■																											
Post-treatment tests and rs-fMRI										■																										
Maintenance tests												■			■																					
Data analysis											■		■			■																				
AIM 2																																				
Pre-treatment rs-fMRI in group 3			■																																	
Post-treatment rs-fMRI in group 3										■																										
AIM 3																																				
Meeting with professionals																	■																			
Development of device																		■	■	■	■	■	■													
Pre device tests and rs-fMRI																								■												
Device tests																									■	■	■	■	■	■	■					
Post device tests and rs-fMRI																																■				
Maintenance rs-fMRI and test																																			■	
Analysis data																																	■			■