A PROPOSAL FOR INNOVATIVE TREATMENTS FOR TINNITUS

‘WAR ON TINNITUS’

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EXECUTIVE SUMMARY

TEAM

Dirk De Ridder, Professor Neurosurgery, University Otago, Co-Founder BRAI3N-Centre for neuromodulation, Ghent

Divya Adhia, Matt Hall, research fellows at University of Otago

Brai3n Clinic, Gent, Belgium & Research Unit University of Otago, New Zealand

GOAL

A highly innovative approach to finding a solution for tinnitus in a short time frame, i.e., 3 to 5 years. To reduce and ideally abolish the sound in contrast to most tinnitus studies that attempt to reduce the suffering associated with the tinnitus.

CONCEPT OF WAR RESEARCH APPROACH

This approach has been proven highly successful in fighting AIDS. Our approach is to develop treatments based on the concept of war, on how a war is fought: use whatever available relevant scientific information exists to create a strategy that is multimodal and surprising. The surprising approach is essential because traditional evidence-based approaches have so far failed to develop any FDA or CE approved treatments after many years of tinnitus research.

FOCUS

The brain is the generator of tinnitus, even when triggered from the ear.

- 8 different research approaches.
- 4- year period
- Total cost of €690.000
- Interim evaluation after 2 years.

TINNITUSFREE

With coordination and support of the TinnitusFree Foundation.

GOAL

This proposal is an innovative, high gain approach to finding a solution for tinnitus on a short time frame, i.e., 3 to 5 years, but all proposals are easy to roll out in tinnitus clinics if proven successful. The goal is to reduce and ideally abolish the sound in contrast to most tinnitus studies that attempt to reduce the suffering associated with the tinnitus.

BACKGROUND

The brain is the generator of tinnitus, even when triggered from the ear[1]. Tinnitus is the not the consequence of one brain area (auditory cortex) going in overdrive, as previously thought[2], but is to be seen as an emergent property of dysfunctional interactions of multiple interacting networks[3-5]. One network generates the abnormal sound, i.e. tinnitus, other co-activated networks generate the suffering (anxiety, depression,...), and still others disability such as cognitive dysfunction (memory, concentration, attention, ... problems). It is based on genetic and environmental risk factors, which induce epigenetic (=gene expression) and microbiome changes, that combined create a pro-inflammatory state turning transient.

Genetic factors

Immune response

Cytokines: *IL1, TNF*

Nervous system

Neurotransmitters: SLC6A4, GRM7, NAT2

Growth factors: GDNF, BDNF

Ion channels: KCNE1, ADD1

Microbiome

Epigenetics

Neuroinflammation

Environmental factors

Psychological stress

Physical stress

Auditory trauma

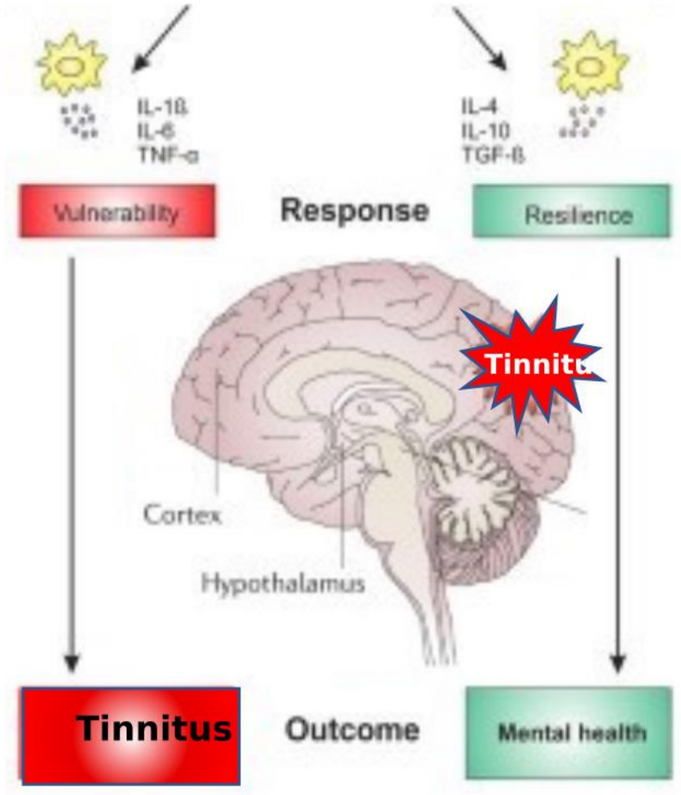
Noise exposure

Chemical exposure

Medication

Drugs: alcohol, cannabis, tobacco

Toxins: Chromium, Cadmium, Manganese



HELLO!

I AM DIRK DE RIDDER

Professor Neurosurgery, University Otago

Co-Founder BRAI3N-Centre for Neuromodulation, Ghent

TREATMENT DEVELOPMENT APPROACH:

‘WAR ON TINNITUS’

Our approach is to develop treatments based on the concept of war, on how a war is fought: use whatever available relevant scientific information exists to create a strategy that is multimodal and surprising. The surprising approach is essential because traditional evidence-based approaches have so far failed to develop any FDA or CE approved treatments after many years of tinnitus research. Multimodal means combining different ways to attack the problem, e.g. sound treatment + psychedelics, multitarget brain stimulation, anti-inflammatory approaches, combining transcranial photo biomodulation with neuromodulation approaches etc. This is analogous to a war being fought by a combination of ground troops, air force and navy. This approach has been proven highly successful in fighting AIDS. By using 4 different drugs that each work on a different mechanism survival has increased from 5 years with 1 drug, to 20 years with 2, 40 with 3 and a normal life expectancy with 4 drugs[7].

If one or more of the proposed studies shows a positive effect the possibility arises to combine them in a new study, i.e., increase the multimodality. By performing studies that use neuromodulation, psychedelics, sound therapy and anti-inflammatory approaches, it increases the chances that we can subsequently combine the different therapies in a truly multimodal approach.

THIS APPROACH HAS BEEN PROVEN HIGHLY SUCCESFUL IN FIGHTING AIDS

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If the outcome of the studies is below expectation, this means that different tinnitus subgroups exist (that are currently unknown), and we need to resort to more individualized studies, in which genome, microbiome and cytokines need to be determined in each individual to create tailor-made treatments for the individual (see appendix). This personalized information can then supplement the individual brain state as measured by EEG or fMRI to address the tinnitus in a truly personalized multimodal approach, adjusting the brain stimulation to the EEG, the medication to the genome, the pre-, pro-or antibiotics to the microbiome, and anti-inflammatory drugs or food supplements to the cytokine profile. This is of course exponentially more expensive and less practical to introduce on a large scale, but still feasible in a larger multidisciplinary tinnitus clinic.

PROPOSAL

Based on the concept that there may exist a final common pathophysiological pathway common to all tinnitus patients, we envision to develop 9 novel treatment approaches, applying the war on tinnitus (multimodal) rationale.

TREATMENT DEVELOPMENT APPROACH:

‘WAR ON TINNITUS’

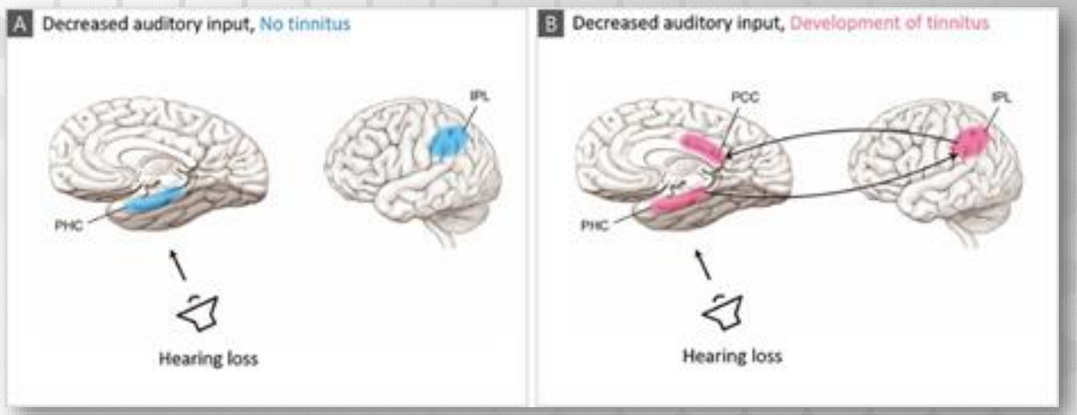
1. Tinnitus core disruption by non-invasive transcranial grey noise stimulation

Background: a tinnitus core network (PCC, Para hippocampus, auditory cortex) has been described based on the difference in brain networks in people with hearing loss without tinnitus and people with the same hearing loss who do have tinnitus[8].

Goal: disrupt tinnitus network with electrical noise stimulation. If the network falls apart the tinnitus should disappear, as tinnitus is an emergent property of a 'tinnitus network'.

Study: test 20 patients with noise stimulation versus placebo, 3 session a week for 3 weeks (= 9 sessions) using the Neuro-electrics device that uses a 32-channel stimulator that can perform network stimulation (see image), based on computer simulations of current flow on a standard head model

Desired outcome: reduction/disappearance of tinnitus



32-channel Starstim Neuro-electrics transcranial electrical brain stimulator

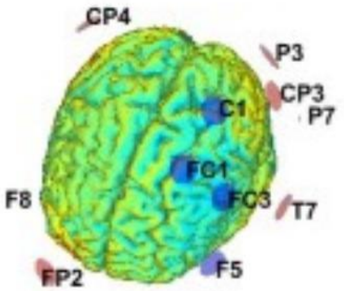
Active montage

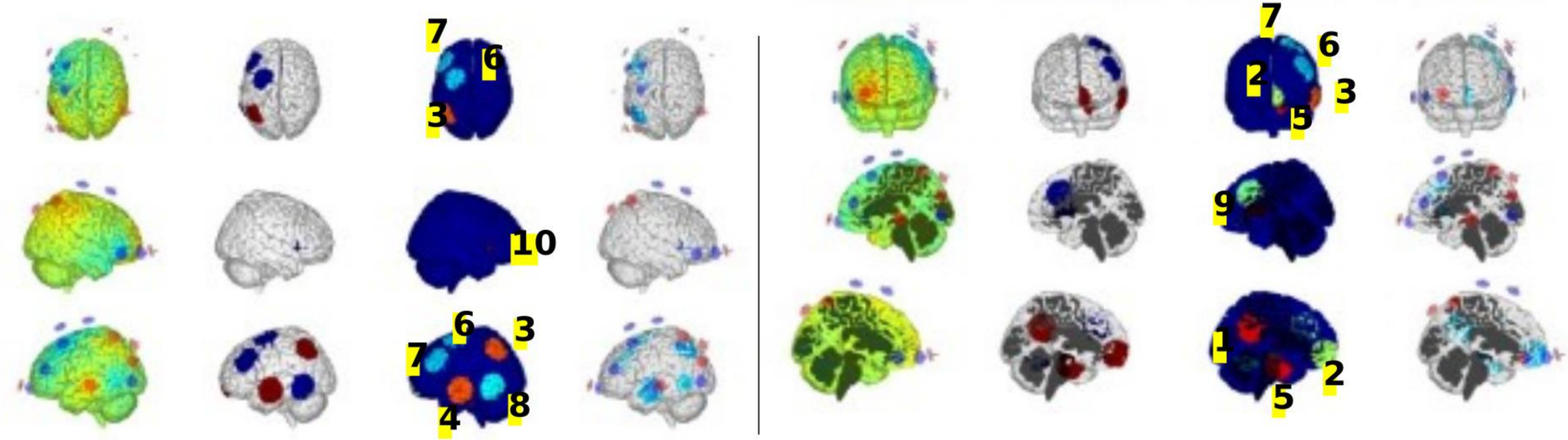
11 electrodes
Total injected current (mA): 3797uA
Maximum current any electrode (mA): 1399uA

Fitness function (ERN): -4137.005mV^2/m^2 (98%)
WCC: 0.283 (98%)

C1: -452uA
CP3: 511uA
CP4: 869uA
F5: -432uA
F8: -1231uA
FC1: -328uA
FC3: -513uA
FP2: 1399uA
P3: 328uA
P7: -841uA
T7: 690uA

Idx	w5	<nE>(V/m)	
1	17	0.010	
2	10	0.021	
3	15	0.018	0.013
4	15	0.012	
5	17	0.003	
6	6	-0.038	
7	6	-0.032	
8	7	-0.024	-0.024
9	9	-0.013	
10	19	-0.007	





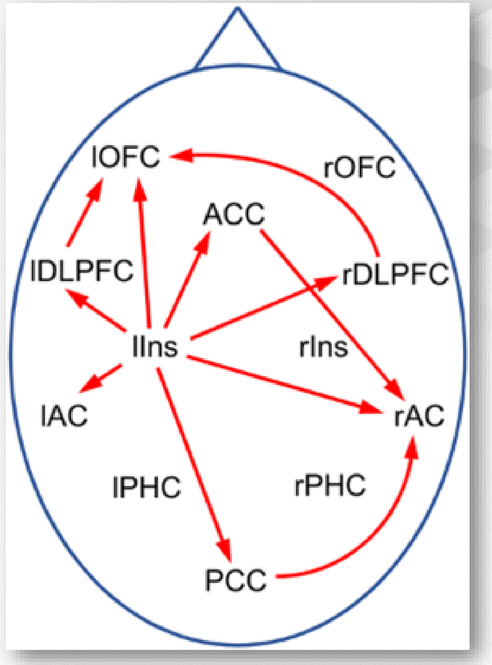
2. Transcranial electrical insula stimulation versus transcranial electrical insula + tinnitus core network stimulation

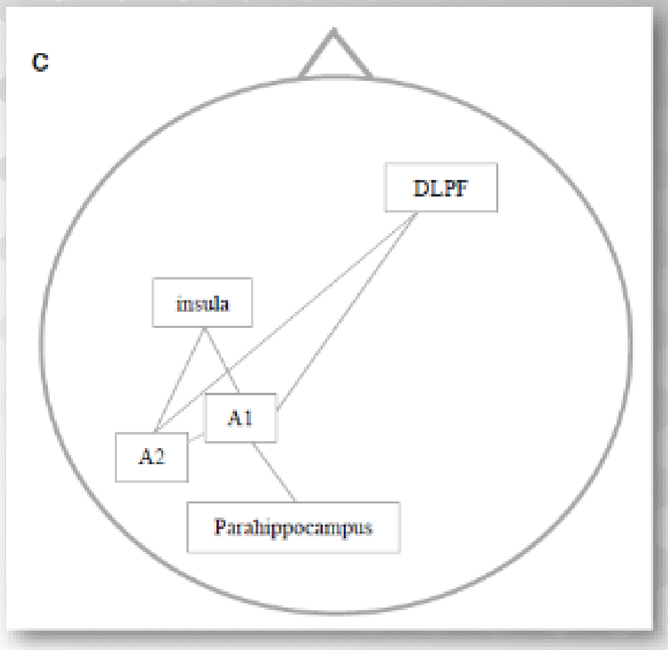
Background: the insula, which is part of the salience (= behavioral relevance) network sends out information that tells the rest of the brain that the tinnitus is salient, i.e behaviorally relevant9 (left figure, lIns = left Insula). The insula is part of the chronic tinnitus network10 (right figure)

Goal: disrupt insula to send information to tinnitus network and compare this to disrupting insula plus the rest of chronic tinnitus network, i.e. insula + DLPFC + Para hippocampus + auditory cortex (right figure).

Study: test 20 patients, 10 patients in each group using noise stimulation generated by the 32 channel Neuro-electrics stimulator to disrupt the pathological connections (see above).

Expected outcome:
reduction/disappearance of tinnitus





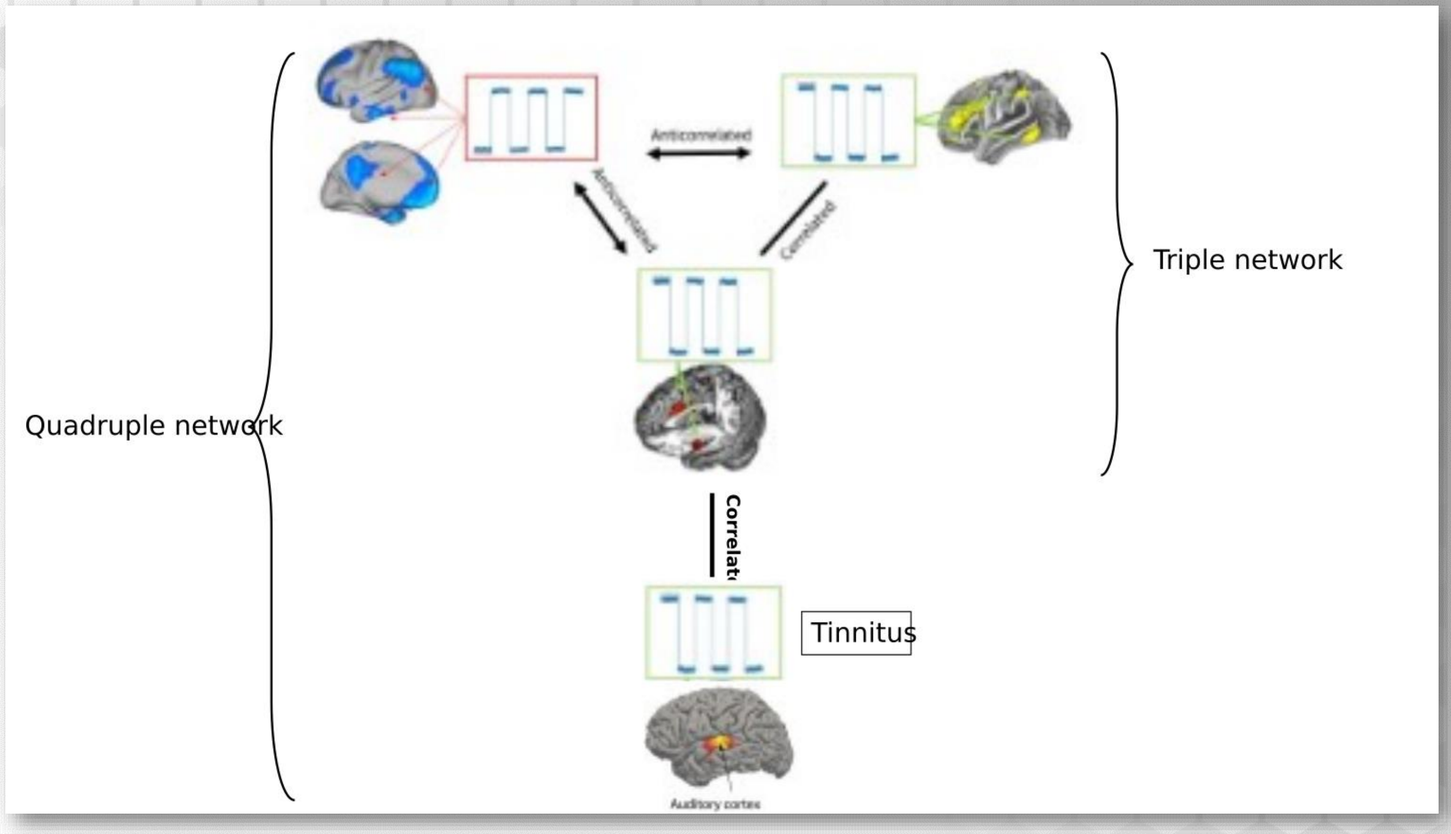
3. Quadruple network stimulation

Background: a sound stimulus activates the auditory cortex in patients who are conscious but also in patients who are unconscious[11].

For a sound to become conscious the auditory cortex needs to be connected to consciousness enabling networks[12]. These consist of the default mode network (DMN), integrating the tinnitus in the self, and the central executive network (CEN)[13]. But the sound will only persist if the brain deems it salient (=behaviourally relevant).

Indeed, a sound is perceived if the salience network (SN) is co-activated[14]. These 3 networks constitute the triple network, involved in almost all studied brain disorders[15]. Integrating the core tinnitus network into the triple network model we need to target a quadruple network, i.e. the triple network + auditory cortex[4].

We developed a triple network stimulator that normalizes the activity and communication within and between the 3 networks (not yet published), that we can extend to the auditory cortex, i.e. quadruple network stimulation (figure).



Goal: disrupt quadruple network, i.e. disrupt the connections between the DMN, SN, CEN and auditory cortex

Study: test in 20 patients vs placebo using the Neuro-electrics 32 channel transcranial electrical stimulator, 3 sessions per week for 3 weeks

Expected outcome: reduction/disappearance of tinnitus

4. Transcranial rebalancing electrical stimulation

Background: it has been proposed that tinnitus is the result of a balance between 2 tinnitus provoking networks (lateral sound pathway and medial suffering pathway) and 1 tinnitus suppressing network, aka the noise canceling network5 (figure).

Goal: normalize the imbalance by suppressing the 2 tinnitus provoking networks and activating the noise cancelling network, analogous to what has been shown in pain6.

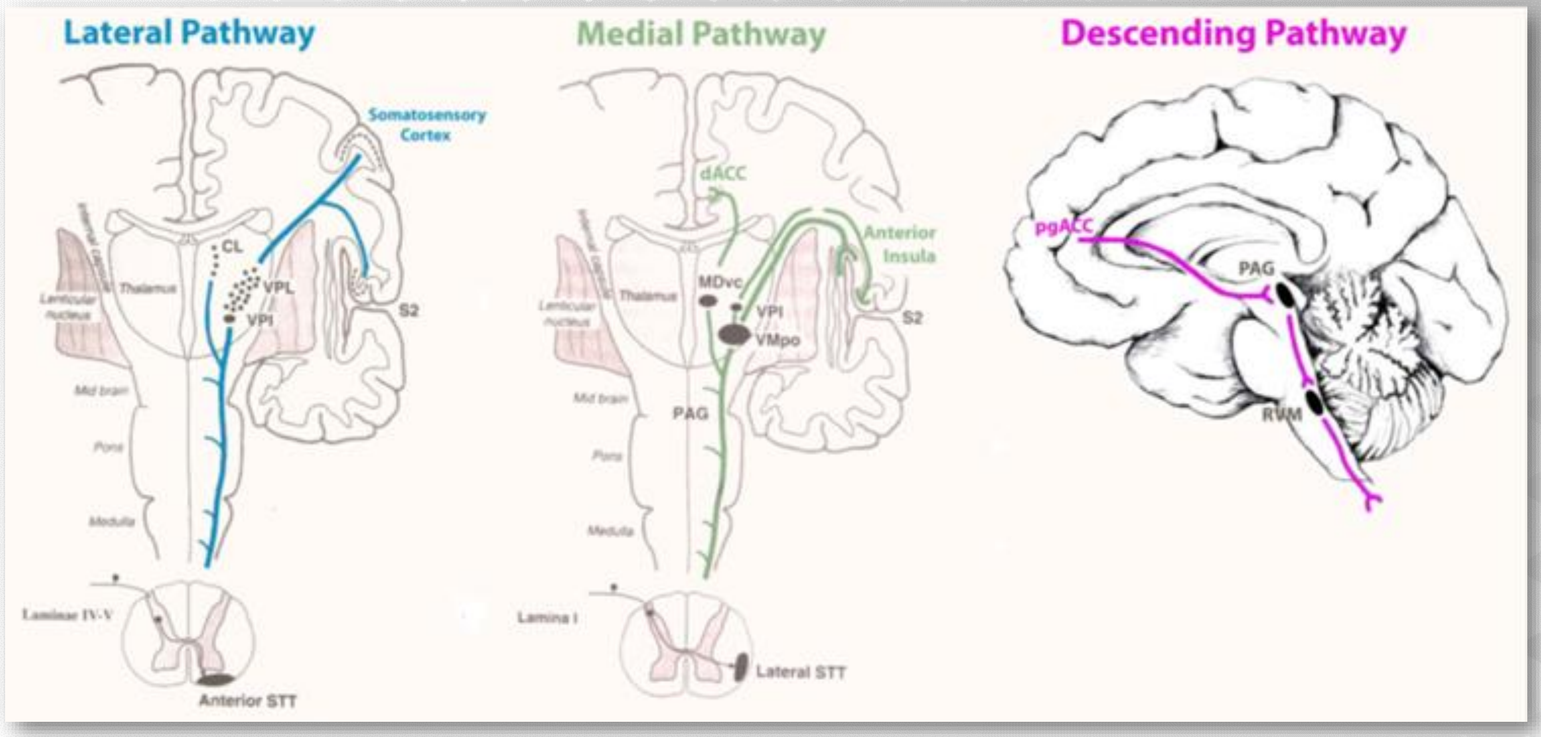
Study: rebalance the 3 networks, using the 32-channel network stimulator. This can be achieved by using inhibitory cathodal stimulation of the 2 activating networks and activating anodal stimulation of the noise cancelling network

Expected outcome: reduction/disappearance of tinnitus

Specific Ascending SOUND pathway

Non-specific Ascending SUFFERING pathway

Noise cancelling Inhibitory pathway



5. Transcranial electrical stimulation + psychedelics (MMDA)

Background: psychedelics transiently increase the communication (=connectivity) between many areas in the brain[16], hence the ego dissolution and blissful state. Furthermore, MDMA can open the critical period[17], a period after birth associated with increased neuroplasticity (=capacity for adaptation of the brain). This is successfully used in PTSD (posttraumatic stress syndrome)[18].

Goal: induce increased neuroplasticity, i.e. malleability of the brain, by MDMA, followed by quadruple network normalization to restore the connectivity as before the tinnitus

Study: test in 20 patients: quadruple network neurostimulation + MDMA vs quadruple network stimulation without MDMA, using the 32 channel Neuroelectric stimulator

Expected outcome: reduction/disappearance of tinnitus

6. Sound treatment + MDMA

Background: psychedelics transiently increase the communication (=connectivity) between many areas in the brain[16], hence the ego dissolution and blissful state. Furthermore, MDMA can open the critical period[17], a period after birth associated with increased neuroplasticity (=capacity for adaptation of the brain). This is successfully used in PTSD (posttraumatic stress syndrome)[18].

Goal: when the tinnitus becomes irrelevant due to the blissful state while presenting tinnitus tones, the brain should suppress the irrelevant tinnitus (like we don't feel our clothes because it is irrelevant).

Study: present tinnitus tones under 125 mg of MDMA in 3 sessions, once per week

Expected outcome:
reduction/disappearance of tinnitus or habituation to the tinnitus, i.e. making it not bothersome

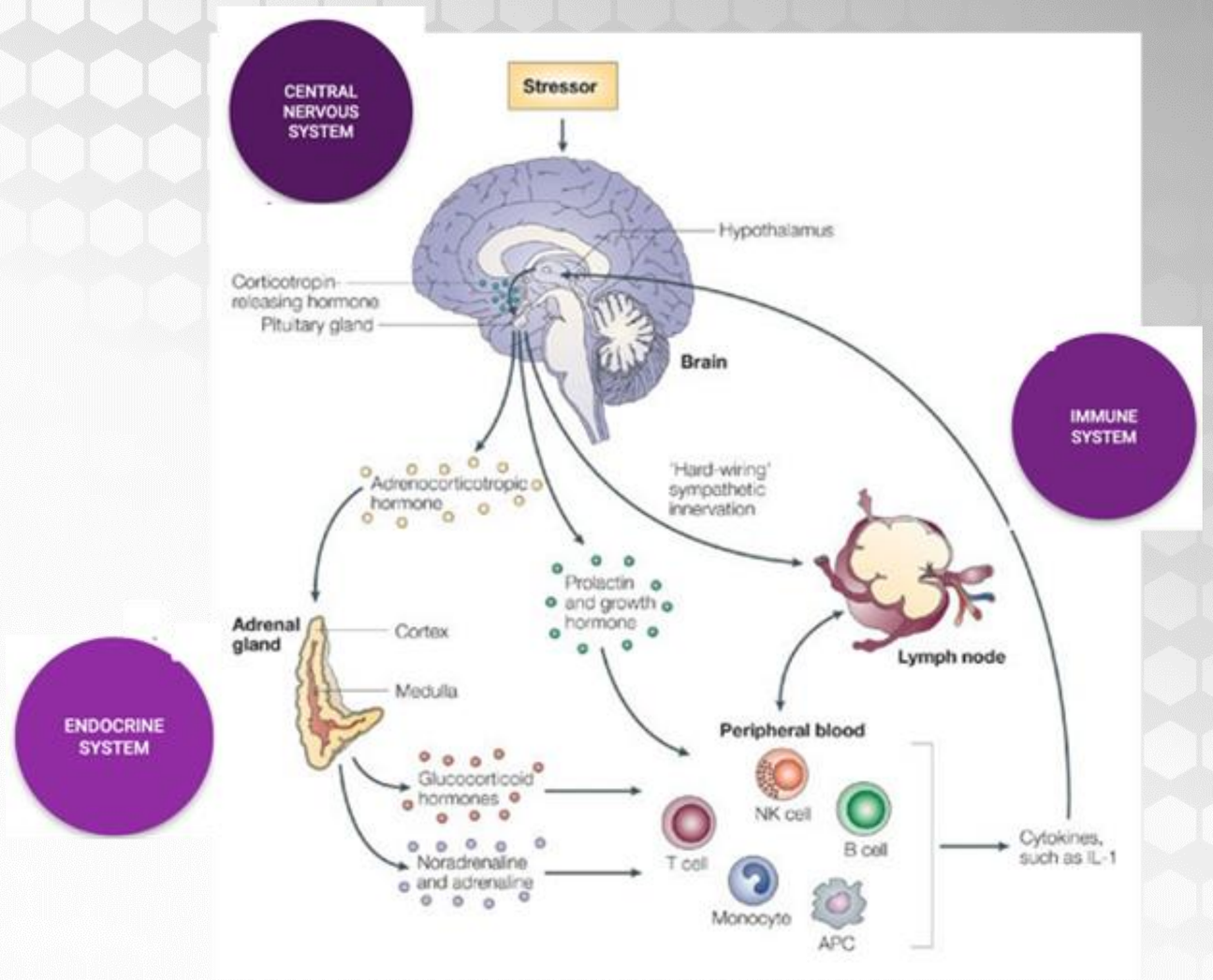
7. Treatment of tinnitus with anti-inflammatory food supplements

Background: acute tinnitus becomes chronic when arising during a pro-inflammatory state[20], as in stress. In stress the hypothalamus may become inflamed[21], which modifies the interaction between the nervous system, endocrine (hormonal) system and immune system[22]. This changes sympathetic versus parasympathetic balance that will result in a persistent pro-inflammatory state, resulting in chronification of acute pathology.

Goal: stop hypothalamic inflammation to normalize interaction between brain, immune and endocrine system. The yellow dahlia flower contains 3 substances (butein, isoliquiritigenin, sulfuretin) that together create an anti-inflammatory effect that is capable of completely abolishing a hypothalamic inflammation in animals (Alexander Tubs, in press).

Study: comparative study 1 month of twice daily Dahlia4TM versus placebo in 20 patients with chronic tinnitus

Expected outcome: reduction/disappearance of tinnitus or habituation to the tinnitus, i.e. making it not bothersome



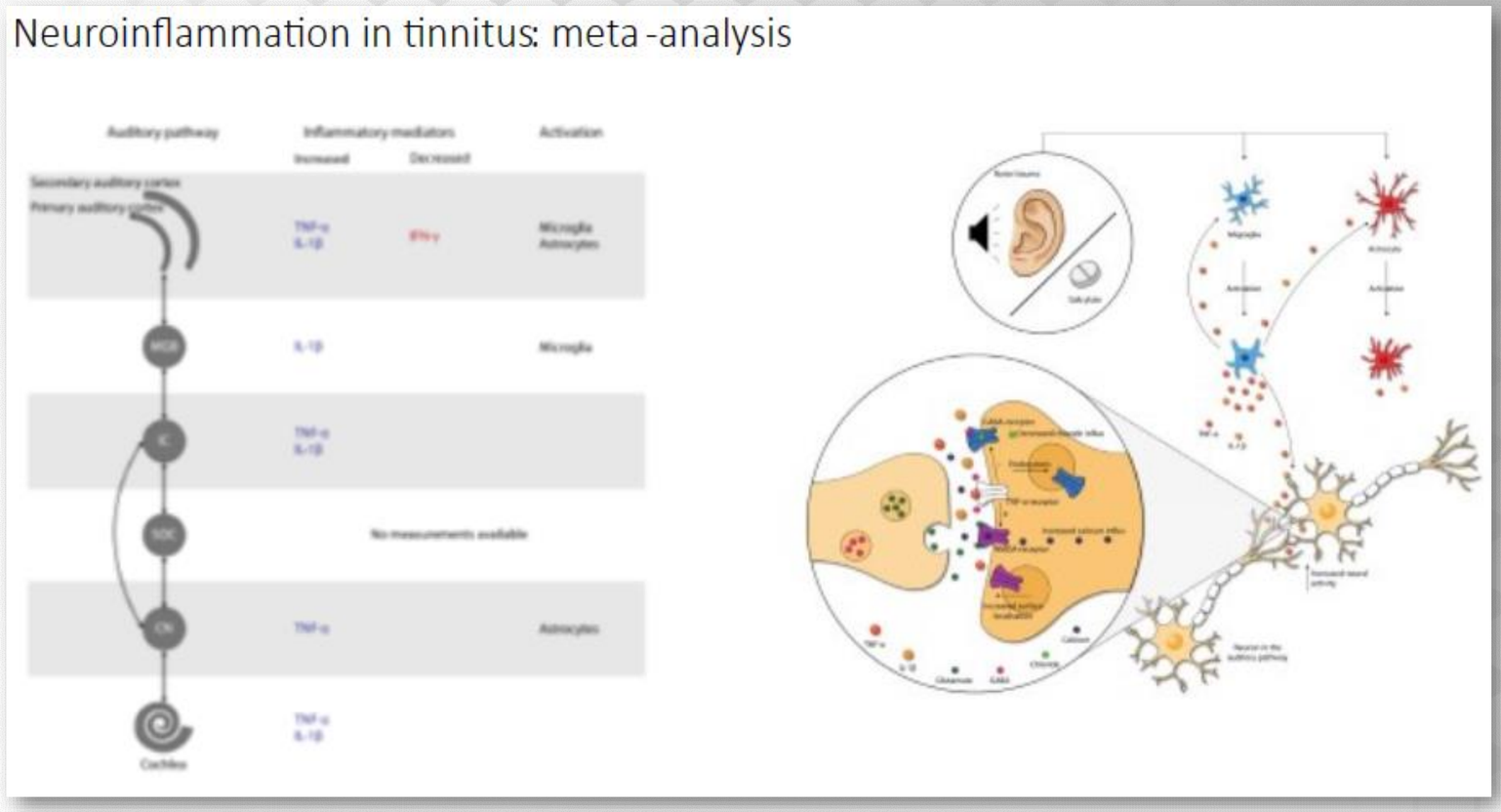
8. Treatment of tinnitus with anti-inflammatory medication

Background: chronic tinnitus is associated with a low grade neuroinflammation in the auditory pathways, from cochlea to auditory cortex[20]. The 2 most relevant pro-inflammatory cytokines expressed at all levels of the auditory pathway are TNFα and IL1β.

Goal: stop auditory payhway inflammation to eliminate chronification of tinnitus

Study: comparative study 1 month of TNFα blocker versus placebo in 20 patients with chronic tinnitus

Expected outcome: reduction/disappearance of tinnitus or habituation to the tinnitus, i.e. making it not bothersome



9. Photobiomodulation + other treatment

Background: photo biomodulation consists of applying laser or LED light to the brain at frequencies between 780 nm and 2500 nm, which is known to penetrate the skull[23], as it is used as a functional imaging tool (= fNIRS). The mechanism of action is related to the generation of more energy (ATP) in the mitochondria[24]. It has been shown that transcranial light stimulation (= photo biomodulation) can improve cognitive function[25].

Goal: based on the triple network model for cognitive function that we have extended to the quadruple network[4], incorporating photo biomodulation should enhance the benefit of the quadruple network treatment, especially in patients who have cognitive problems due to exhaustion caused by chronic tinnitus associated stress. This exhaustion can result in atrophy of the stress network (=salience network)[26]. And indeed, in patients with anxiety and depression the insula is atrophic[27], due to excitotoxicity (=exhaustion).

Study: test 20 patients with the Neuradiant 1070 nM photobiomodulation device, 10 patients with severe tinnitus associated with cognitive disfunction with photobiomodulation prior to quadruple network stimulation versus 10 patients with only quadruple network stimulation (without photobiomodulation, ie, with placebo photobiomodulation).

Expected outcome: patients who might not respond to quadruple network stimulation because the brain is exhausted (=chronic fatigue) may benefit from the combined approach

BUDGET

COST FOR TOTAL PROGRAM: €690.000
COST FOR 1st PHASE: €345.000

The cost of this tinnitus research program can be reduced by simultaneously performing multiple studies. This reduces the cost for research assistants and/or PhD students. If all 8 studies need to be performed 3 research assistants are needed for 2-3 years. One research fellow (postdoc) is required to supervise these studies as Prof De Ridder is not onsite in New Zealand for more than 5 months per year. However, the cost of research assistants, PhD students and research fellows is substantially lower than in the EU, and ethical approval has up till now never been refused for our brain stimulation studies, even though it takes 3 months to get ethical approval. For each stimulation protocol Neuro-electrics needs to develop a custom-made design, based on computer simulations. These cost 5000 euro per design (on average). In New Zealand study participants are reimbursed for travel costs. Medical grade MDMA is very expensive, 26,500 USD for 20 gram. The Neuradiant device costs 5000 USD (with placebo possibility).

A detailed budget is available on request.

REFERENCES

1. De Ridder D, Elgoyhen AB, Romo R, Langguth B. Phantom percepts: tinnitus and pain as persisting aversive memory networks. *Proc Natl Acad Sci U S A.* 2011;108(20):8075-8080.
2. Llinas RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc Natl Acad Sci U S A.* 1999;96(26):15222-15227.
3. De Ridder D. A heuristic pathophysiological model of tinnitus. In: Moller A, Langguth B, De Ridder D, Kleinjung T, eds. *Textbook of Tinnitus.* New York: Springer; 2011:171-198.
4. De Ridder D, Vanneste S, Song JJ, Adhia D. Tinnitus and the triple network model: a perspective. *Clin Exp Otorhinolaryngol.* 2022.
5. De Ridder D, Vanneste S. The Bayesian brain in imbalance: Medial, lateral and descending pathways in tinnitus and pain: A perspective. *Prog Brain Res.* 2021;262:309-334.
6. De Ridder D, Adhia D, Vanneste S. The anatomy of pain and suffering in the brain and its clinical implications. *Neurosci Biobehav Rev.* 2021;130:125-146.
7. Trickey A, Sabin CA, Burkholder G, et al. Life expectancy after 2015 of adults with HIV on long-term antiretroviral therapy in Europe and North America: a collaborative analysis of cohort studies. *Lancet HIV.* 2023;10(5):e295-e307.
8. Lee SY, Chang M, Kwon B, et al. Is the posterior cingulate cortex an on-off switch for tinnitus?: A comparison between hearing loss subjects with and without tinnitus. *Hear Res.* 2021;411:108356.
9. Zobay O, Palmer AR, Hall DA, Sereda M, Adjamian P. Source space estimation of oscillatory power and brain connectivity in tinnitus. *PLoS One.* 2015;10(3):e0120123.
10. Vanneste S, van de Heyning P, De Ridder D. The neural network of phantom sound changes over time: a comparison between recent-onset and chronic tinnitus patients. *Eur J Neurosci.* 2011;34(5):718-731.
11. Laureys S, Faymonville ME, Degueldre C, et al. Auditory processing in the vegetative state. *Brain.* 2000;123 (Pt 8):1589-1601.
12. Demertzi A, Soddu A, Laureys S. Consciousness supporting networks. *Curr Opin Neurobiol.* 2012.
13. Akeju O, Loggia ML, Catana C, et al. Disruption of thalamic functional connectivity is a neural correlate of dexmedetomidine-induced unconsciousness. *Elife.* 2014;3:e04499.
14. Sadaghiani S, Hesselmann G, Kleinschmidt A. Distributed and antagonistic contributions of ongoing activity fluctuations to auditory stimulus detection. *J Neurosci.* 2009;29(42):13410-13417.
15. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci.* 2011;15(10):483-506.
16. Tagliazucchi E, Roseman L, Kaelen M, et al. Increased Global Functional Connectivity Correlates with LSD-Induced Ego Dissolution. *Curr Biol.* 2016;26(8):1043-1050.
17. Nardou R, Lewis EM, Rothhaas R, et al. Oxytocin-dependent reopening of a social reward learning critical period with MDMA. *Nature.* 2019;569(7754):116-120.
18. Mithoefer MC, Wagner MT, Mithoefer AT, et al. Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. *Journal of psychopharmacology.* 2013;27(1):28-39.
19. De Ridder D, Schlee W, Vanneste S, et al. Tinnitus and tinnitus disorder: Theoretical and operational definitions (an international multidisciplinary proposal). *Prog Brain Res.* 2021;260:1-25.
20. Mennink LM, Aalbers MW, van Dijk P, van Dijk JMC. The Role of Inflammation in Tinnitus: A Systematic Review and Meta-Analysis. *J Clin Med.* 2022;11(4).
21. Cernackova A, Durackova Z, Trebaticka J, Mravec B. Neuroinflammation and depressive disorder: The role of the hypothalamus. *J Clin Neurosci.* 2020;75:5-10.
22. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. *Nat Rev Immunol.* 2005;5(3):243-251.
23. Henderson TA, Morries LD. Near-infrared photonic energy penetration: can infrared phototherapy effectively reach the human brain? *Neuropsychiatr Dis Treat.* 2015;11:2191-2208.
24. Kitchen LC, Berman M, Halper J, Chazot P. Rationale for 1068 nm Photobiomodulation Therapy (PBMT) as a Novel, Non-Invasive Treatment for COVID-19 and Other Coronaviruses: Roles of NO and Hsp70. *Int J Mol Sci.* 2022;23(9).
25. Lee TL, Ding Z, Chan AS. Can transcranial photobiomodulation improve cognitive function? A systematic review of human studies. *Ageing Res Rev.* 2023;83:101786.
26. Qiu Y, Fan Z, Zhong M, et al. Brain activation elicited by acute stress: An ALE meta-analysis. *Neurosci Biobehav Rev.* 2021.
27. Goodkind M, Eickhoff SB, Oathes DJ, et al. Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry.* 2015;72(4):305-315.

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