Investigating GABAergic inhibition in tinnitus with GABA-edited magnetic resonance spectroscopy and 11C-Flumazenil positron emission tomography.

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Primary Objective: The primary objective is to compare GABA concentrations and receptors availability in the auditory pathway between individuals with tinnitus and two control groups without tinnitus (with or without hearing loss). GABA...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hearing disorders
Study type	Observational invasive

Summary

ID

NL-OMON55068

Source
ToetsingOnline

Brief title
GABAergic inhibition in tinnitus

Condition

- Hearing disorders

Synonym
Ringing in the ears, Tinnitus

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: GABAergic inhibition, Hearing loss, Tinnitus

Outcome measures

Primary outcome

The main study parameters are the GABA concentrations and GABA(A) receptors availability (binding potential) in the auditory pathway as measured with GABA-edited MR spectroscopy and with [11C]-flumazenil PET respectively.

Secondary outcome

Secondary study parameters include (1) the functional connectivity at rest and during sound stimulation as assessed with (partial-) correlations between activity time courses, (2) the level of activity in the auditory pathway at rest (i.e. spontaneous activity) and during sound perception, (3) the correlations between GABA levels and the functional connectivity as well as the spontaneous activity in the auditory pathway. We predict that compared to the other two groups, the tinnitus group will show enhanced spontaneous activity in nodes of the auditory pathway as well as decreased functional connectivity between these nodes.

Study description

Background summary

Tinnitus is a prevalent condition characterised by the perception of a sound in

the absence of external stimulation. Approximately 15% of the world population experience tinnitus. For the large majority (80%), tinnitus is associated with hearing-loss in the same frequency range as the perceived phantom sound. In 10 to 20% of individuals this ringing in the ears results in a significant decrease in quality of life. To date there is no cure for tinnitus and most interventions consist in deploying coping strategies (Bauer, 2018). The main challenge for developing an effective treatment is the lack of understanding of the neuropathological mechanisms underlying this condition.
Tinnitus is thought to be triggered by changes in the central auditory system following peripheral insults or sensory deprivation (Knipper et al., 2013; Noreña and Farley, 2013). In this perspective, reduced peripheral sensory input would activate homeostatic plasticity mechanisms, and maladaptive homeostasis would lead to tinnitus in a proportion of individuals. Homeostasis of neuronal circuits depends on a good balance between neuronal excitation and inhibition. Several lines of evidence from animal studies suggest that differences in GABAergic inhibition may relate to tinnitus per se. Firstly, several studies found that drugs enhancing GABAergic inhibition abolish the tinnitus behavior in animals (Brozoski et al., 2007; Lu et al., 2011; Yang et al., 2011). This does not seem to be the case of drugs diminishing excitatory neurotransmission (Yang et al., 2011). In one study, increasing GABA concentration was further associated with a normalization of sound-evoked response in AC (Lu et al., 2011). Secondly, in AC and IC, inhibitory neurotransmission is reduced in neurons that represent the hearing-loss frequency range (Dong et al., 2010; Yang et al., 2011). Thirdly, in the auditory thalamus increased GABA mediated tonic inhibition was found in rats with behavioral evidence of tinnitus by comparison to hearing-impaired rats with no sign of tinnitus (Sametsky et al., 2015). Finally, a recent study compared the effect of noise trauma in two strains of mice, one of which demonstrating evidence of tinnitus, the other not (Miyakawa et al., 2019). A reduction of GAD65 (a GABA-synthesizing enzyme in the synapse) was found only in the strain that developed tinnitus. Crucially, knocking down GAD65 in normal-hearing mice of the strain that did not normally develop tinnitus following noise trauma induced tinnitus behavior. All these studies suggest a crucial role of GABA in the development of tinnitus.
Importantly enough, a recent study found a causal link between tinnitus, increased spontaneous firing rate and decreased GABAergic neurotransmission in AC (Hayes et al., 2021). The authors found that decreasing GABAergic inhibition with a drug that blocks GABA(A) receptors (Gabazine) caused tinnitus behaviour in naive animals and was associated with increased spontaneous firing rates of auditory cortex neurons. The authors further demonstrate that no any other changes in the auditory pathway following noise trauma or salicylate exposure could be linked to tinnitus univocally. This study provides strong support to theories that have attributed tinnitus to increased spontaneous firing rate in the auditory pathway as a direct consequence of decreased GABAergic inhibition (Wang et al., 2011; Richardson et al., 2012).
Despite the overwhelming evidence for a role of GABAergic inhibition in the pathophysiology of subjective tinnitus, only one single study to date has investigated GABA levels in humans affected by this condition (Sedley et al.,

2015). The authors used Magnetic Resonance Spectroscopy (MRS) to evaluate GABA concentrations in the auditory cortex. They reported decreased GABA concentrations in the right AC of subjects with tinnitus compared to a group matched for hearing levels.
With our research project we hope to advance our understanding of GABAergic neurotransmission in tinnitus. A better understanding of the molecular changes occurring in the auditory pathway in association with hearing loss and tinnitus is an essential step towards the development of a medicine.

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Study objective

Primary Objective:
The primary objective is to compare GABA concentrations and receptors

availability in the auditory pathway between individuals with tinnitus and two control groups without tinnitus (with or without hearing loss). GABA concentrations will be measured with MR spectroscopy, and GABA(A) receptors availability with [11C]-flumazenil PET.

Secondary Objectives:
We further want to test for an association between measures of GABA levels and the activity and functional connectivity of the auditory pathway. We will investigate activity and functional connectivity between these regions both during sound perception and at rest with fMRI. Furthermore with PET we will measure cerebral blood flow at rest in a quiet environment, which will provide an indication of spontaneous activity in the auditory pathway. We predict that (1) spontaneous brain activity is increased in the auditory cortex of individuals with tinnitus, and (2) increased spontaneous activity in AC is associated with lower levels of GABA. In addition, since spontaneous activity corresponds to noise, we predict that (3) differences in GABAergic neurotransmission in AC will be associated with decreased functional connectivity between AC and the auditory thalamus and inferior colliculus.

Study design

The study is composed of 3 sessions: Audiological assessment, MRI scanning, and PET scanning. The last session is facultative and will involve a subsample of 45 participants who completed the MRI session (15 per group).
1) Audiometry and questionnaires
Before being included in the study, participants will first receive an audiometric test, and will fill questionnaires about tinnitus, hyperacusis, handedness, and anxiety/depression. The tinnitus questionnaire is filled only by participants with tinnitus. Participants with tinnitus will also perform a tinnitus sound matching procedure. The total duration of these tests and questionnaires will be about 60 minutes. An appointment will then be made within three months for the MRI scanning.
2) MRI scanning
Participants will then undergo an MRI scanning session comprising GABA-edited MRS, an anatomical scan, two resting-state scans, and a sound-evoked fMRI scan. The total duration of the MRI scanning session is 120 min, including a 20 min break and 10 min for moving the participant in and out the scanner.
3) PET scanning
A subset of volunteers will be invited to further undergo a PET scan, which will permit to measure GABA receptors availability in the auditory cortices as well as in smaller midbrain structures. The PET scan will not take place more than 3 months after the MRI scanning. The total duration of Part-2 will be 90 min including participant preparation and PET scanning. The lower number of participants included in Part-2 owes to the cost and burden of PET-scanning, and it will not impede on our ability to detect group differences. Participants will be selected on a first-come first-served basis for the PET scanning. When all the slots have been filled, new participants will be notified that there is

no more spot available for this part at the same time as they receive the information letter.

The study will take place at the University Medical Centre Groningen; ENT department for the audiogram and questionnaires, Radiology department for the MRI scanning, and department of Nuclear Medicine and Molecular Imaging for the PET scan.

Study burden and risks

Participants in the study will be given an audiometry test (20 min) and answer 5 short questionnaires (30 min). Participants with tinnitus will also perform a tinnitus sound matching task (10 min). These tests and questionnaires do not involve more than minimal risk and are not associated with any particular burden.

The participants will further undergo a 90 min MRI scanning. MRI is a standard brain imaging technique with no known negative effects on health. The only risks are for subjects with cardiac pacemaker and metal implants. These individuals will not be allowed to participate. In terms of burden, MRI involves lying still in a confined environment. In addition, for some sequences the gradient coils generate a banging sound as loud as 100 dB. Participants in the study will be protected by MR compatible internal hear-phones and inflatable cushions covering the ears that together reduce the scanner noise by around 30-40 dB.

The forty-five subjects who volunteer for part-2 of the project will be scanned in a PET scanner after intravenous injection of the [11C]-Flumazenil GABA tracer. The scanning lasts 60 minutes. In terms of safety, the dose of radioactivity being injected (400 Mbq) would correspond to an effective dose of about 3.1 mSv which falls in the lower bounds of the ICRP category II-b of minor to moderate risks (1-10mSv). For comparison, the level of radiation for a single CT scan of the chest is more than two times higher (about 7mSV). The equivalent time of background radiation from the natural environment is less than one year considering an EU average of 3.2 mSv/a. Burdens associated with the PET scan are receiving an intravenous injection and lying still during 60 minutes.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

For all participants:
• Adult, 18 to 75 years of age
• Understanding the study and providing written informed consent
In addition, depending on the group:
• Group-1 (T+HL+): Having chronic tinnitus (for more than 2 months) and mild to moderate hearing loss (pure tone average for frequencies of 4 to 8kHz between 30 and 60dB for both ears).
• Group-2 (T-HL+): Having mild to moderate hearing loss (as above) without tinnitus.
• Group-3 (T-HL-): Having no tinnitus and normal hearing thresholds (pure tone average <= 30 dB for frequencies of 4 to 8kHz, on both ears).

Exclusion criteria

• Not meeting the inclusion criteria of one of the 3 groups (T+HL+, T-HL+, or T-HL-)
• Using hearing aids
• Metal implants incompatible with the MRI scanner magnetic field (e.g.,

pacemaker, heart valves, vascular clips, cerebral implants, eye-implants, intra-uterine devices containing copper, non-removable piercing)
• Any risk of having metal particles in the eyes
• Tattoos containing iron oxide
• Claustrophobia
• History of neurological or neuropsychiatric illness (apart from tinnitus and hearing loss)
• Being pregnant or at risk from being pregnant
• Breastfeeding
• Use of psycho-active medications (e.g., benzodiazepine, SSRI)
• Alcohol or drug abuse
• Refusal to be informed of structural brain abnormalities that could be detected during the experiment

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-10-2021
Enrollment:	90
Type:	Actual

Ethics review

Approved WMO

Date:	16-08-2021
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-08-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL74533.042.20