Does Sound Conditioning Protect Against Temporary Hearing Damage?

Research Protocol

Version 8

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MAIN SPONSOR: Imperial College Healthcare NHS Trust

Study Management Group

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Clinical Queries

Clinical queries should be directed to Hemna Santilale who will direct the query to the appropriate person.

Sponsor

Imperial College Healthcare NHS Trust is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building

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http://www3.imperial.ac.uk/clinicalresearchgovernanceoffice

Funder

This research project is part of a MSc. project within the Scientist Training Programme.

This protocol describes this study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator. This study will adhere to the principles outlined in the UK Policy Frame "Work for Health and Social Care Research." It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Table of Contents

GLOSSARY OF ABBREVIATIONS

PTA	Pure Tone Audiometry
DPOAE	Distortion Product Otoacousic Emissions
MEMR	Middle Ear Muscle Reflex
EHF	Extended High Frequency
TFI	Tinnitus Functional Index
SiN	Speech in Noise
HL	Hearing Loss
NIHL	Noise Induced Hearing Loss
WHO	World Health Organisation
NESI	Noise Exposure Structure Interview

STUDY SUMMARY

TITLE Does Sound Conditioning Protect Against Temporary Hearing Damage?

DESIGN Between Groups Trial

AIMS To investigate if previous sound conditioning reduces susceptibility to TTS and tinnitus when comparing to those without prior exposure

OUTCOME MEASURES EHF PTA, DPOAE, MEMR, TFI, SiN Test

POPULATION 40 Normal Hearing, Healthy 18-35 year olds

DURATION July 2019 – May 2020

1. INTRODUCTION

1.1 BACKGROUND

This research project will contribute to the research surrounding the effect on the cochlea after noise exposure; this ever growing field of research has never been more applicable than now with the increase of recreational noise exposure.

Hearing Loss (HL) is becoming more prevalent in today's world, and is the most common sensory deficit. Over 5% of the world's population, over 360 million people, have disabling HL (World Health Organisation [WHO], 2015). This is defined by WHO as a moderate HL where hearing thresholds are greater than 40 dB HL. This figure is expected to be closer to 900 million by 2050. In the U.K. alone, latest figures suggest one in six of the population have some form of HL. By 2035, it is estimated that this will increase to one in five (Action on Hearing Loss [AoHL], 2016).

Noise is the leading cause of preventable hearing loss and second only to presbycusis (age-related hearing loss) for the most common sensorineural hearing deficit. Excessive occupational noise along with recreational noise exposure can cause a devastating disability. In a world where cities never sleep, traffic never stops, phones require devotion and there is constant noise coming from all directions, it is no surprise that noise itself is one of the most common pollutants. Generally, environmental sounds are at safe levels but sounds can become harmful when too loud and worse when they are long-lasting too. As noise damage usually occurs gradually early in life, it is typically not perceived until it worsens with age and becomes more pronounced and noticeable. At this stage it can cause worse debilitating effects i.e. social isolation. In recent research, there is much more focus concerning young people and excessive exposure to recreational noise. On the 3rd of March 2018, World Hearing Day (WHO) focused on 'Hear the future' to highlight preventative measures and management strategies to address the anticipated rise in hearing loss prevalence globally. WHO estimates 1.1 billion young people could be at risk of hearing loss due to unsafe practice listening practices.

Currently, understanding of NIHL is unclear. There is a reliance on clinical Pure-Tone Audiometry (PTA) results typically from 0.25 Hz to 8 kHz to reveal a characteristic dip/notch in the audiogram between 3 kHz and 6 kHz. An expansion of knowledge and understanding of how noise exposure impacts hearing is required, in order to have better preventative measures and treatments in place.

1.2 RATIONALE FOR CURRENT STUDY

One of the mechanisms shown to increase the resistance against Noise Induced Hearing Loss (NIHL) is 'sound conditioning'. Animal studies have found that prior exposure to low level noise over a period of a few weeks can 'condition' the ear. This conditioning then reduces the susceptibility to

high level exposure i.e. strengthening the cochlea. However, the underlying mechanisms are not yet clarified. This conditioning may be related to: increased levels of antioxidant enzymes, neurotropic factors, inhibition of apoptosis along with many other speculations. Speculation has also occurred with regards to conditioning acting systemically or locally. Animal studies in regards to NIHL and conditioning suggest with prior exposure there is less risk than those with little exposure before experiencing one high exposure event. There are gaps however in the knowledge on the effects of conditioning in humans. A study where humans are tested prior and post a high-exposure event with varying previous noise exposure history ('conditioning') is not yet available. The relations between temporary threshold shift (TTS), speech in noise, tinnitus, and sex are currently unknown and require further investigation.

There are many implications of this research. For one it will allow us to understand more about the susceptibility to exposure of sounds and the resistance against NIHL. This will mean that we can enable appropriate interventions if necessary. For example, an individual who is more susceptible due to low prior exposure may be advised that they are at risk, and encouraged to use hearing protection. We will be able to learn more about the impacts of noise with hearing and educate others such as understanding the impacts from high-level exposure.

2. STUDY OBJECTIVES

i) To identify if there is a relationship between previous sound exposure levels and TTS and tinnitus after a single loud noise event.

3. STUDY DESIGN

Type of Study: Basic Science Study, Between Groups Trial
Aim: To investigate if previous sound conditioning reduces susceptibility to TTS and tinnitus when comparing to those without prior exposure.
Purpose: To increase our understanding on the effects of noise exposure.
Duration: Data collection will be completed by February 2020
Participants: 40 normal hearing young (18-35) participants in good general health and fluent in English.
Spilt into groups of two. One group (20, 10f:10m) with previous exposure i.e. nightclubs ++,
the other group (20, 10f:10m) with less exposure measured through NESI.

3.1 STUDY OUTCOME MEASURES

The participants will need to attend three sessions which will take approximately 35 minutes, 105 minutes overall. Participants will be required to attend testing before, after a high exposure event they would usually find themselves in, and a week later to test recovery. The results will be evaluated and available on request by 04/04/2020. The outcome measures are the Extended Frequency (EF) PTA, Distortion Product Otoacousic Emissions (DPOAE), Tinnitus Functional Index (TFI), Middle Ear Muscle Reflex (MEMR) and Speech in Noise (SiN) Test.

3.2 METHODS

Screening - Participants will be asked about the health of their ears and ears will be examined to ensure there are no abnormalities (Otoscopy). A hearing test (PTA) will then be performed; This test will involve participants listening to a series of tones at different pitches and volumes through headphones and participants will press a button whenever they hear a tone. The researcher will also undertake a structured interview to assess noise exposure history (NESI) and the results from the screen will see if you are eligible to participate in this research. With participants consent, if any abnormalities are detected at any point, your GP will be informed with a copy of the results. Participants will subsequently be excluded from the study and information destroyed. Example of NESI question: I'd like you to estimate how noisy it was when you [engaged in the activity] by answering this question: If you and I were 4 feet apart in that situation, which of the following would you need to do to communicate with me? [The interviewer presents the six options from the Speech Communication Table.]

Each session will require 35 minutes (35 x 3 = 105 minutes overall).

SESSION ONE - Prior to noise exposure (continued same day after screening passed if eligible):
Test battery - High frequency audiometry, Distortion Product Otoacousic Emissions, Middle Ear Muscle Reflex, Speech in Noise test, Tinnitus Functional Index (Around 35 minute testing time with breaks if required)

- Extended Frequency Pure Tone Audiometry (~ 8 minutes)
  Similar to Screening, participants will be asked to press the button when they hear a sound through the headphones in a sound proof booth.
- Distortion Product Otoacoustic Emissions (~ 5 minutes)
  A small tip will be placed in participants' ear and they will hear a sound. The tip measures a response from hair cells in the cochlea and they will not need to do anything.
- Middle Ear Muscle Reflex (~ 8 minutes)
  A small tip will be placed in both ears and again a sound heard however this sound will gradually get louder until an involuntary muscle reflex is noted.

- Speech in Noise Test (~ 5 minutes)
  Participants will be asked to repeat back a list of words as best as they can.
- Tinnitus Functional Index (~ 8 minutes)
  Participants will be given a self-report sheet in which they have to fill out aspects of any tinnitus experienced.

SESSION TWO - Exposure at single loud music event (Important that this is part of participants' normal recreational routine, and specifically require that attendance is not prompted by participation in this study): Participants to use sound level meter provided from the Audiology Department at Charing Cross Hospital to measure sound levels inside the loud event.
Morning after exposure: Repeat test battery from session one - Ideally as soon as event is over.

SESSION THREE: 1 week later (recovery): Repeat test battery.

4. PARTICIPANT ENTRY

A poster will be used in the waiting area and staff room of the Audiology department at Charing Cross Hospital. This poster will also be used on social media.

4.1 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. Participants will be provided the consent form and information sheet via email or directly (meeting organised over the phone – Audiology department at Charing Cross Hospital). They will be given a minimum of 24 hours and maximum of 7 days to contact the researcher to go ahead with the study and a date will be organised to sign the consent form and begin screening. In this time, participants can also ask any questions they may have to the researcher via email or phone. The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

4.3 INCLUSION CRITERIA

- 18-35 years old (as age can affect cochlea hair cell function)
- Healthy participants with no significant medical conditions
- 0.25 Hz to 8 kHz PTA in both ears have thresholds $\leq$ 20 dB HL indicating normal hearing
- Otoscopy to ensure no otological abnormalities
- No exposure to abnormally loud sounds in the past 24 hours
- Full capacity to consent

- Able to speak fluent English so information sheets, consent forms and instructions are fully understood
- Previous intention to attend a loud noise event during the course of the study, without the use of hearing protection

4.4 EXCLUSION CRITERIA

- No permanent tinnitus or hyperacusis (sensitivity to loud sounds) which would mean participants are unable to undertake all testing and a high exposure event
- Any contraindications for testing i.e. excessive wax, infections
- One or more frequencies 0.25 Hz to 8 kHz > 20 dB HL in either ear
- Not involved in current research or have recently been involved in any research prior to recruitment

4.5 WITHDRAWAL CRITERIA

A consent form will be obtained prior to commencing the study however participants' may withdraw at any time by notifying the researcher in person or in written form and without providing any reason.

5. ADVERSE EFFECTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 REPORTING PROCEDURES

All adverse events will be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Principal Investigator in the first instance.

5.2.1 NON SERIOUS AEs

All such events, whether expected or not, will be recorded.

5.2.2 SERIOUS AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs. All SAEs should be reported to Ethics Committee where in the opinion of the Principal Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
Fax. attention Emily Frost
Please send SAE forms to:
Charing Cross Hospital Audiology Department
Fulham Palace Road,
London
W6 8RF
Tel:02033111024 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

Participants will receive a week post-exposure test battery to assess recovery. After this, there will be no follow up in the Audiology Department. If abnormal results are highlighted at any stage, participants will be excluded from the study and as consented, a letter containing the results will be sent to the GP. Participants will subsequently be excluded from the study and information destroyed.

7. STATISTICS AND DATA ANALYSIS

The quantitative data will be analysed by the researcher at Charing Cross Hospital, Imperial Healthcare NHS Trust. Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, in line with trust protocol.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.3 CONFIDENTIALITY

The Principal Investigator will preserve the confidentiality of participants taking part in the study. All information which is collected during the research will be kept strictly confidential. Participants will be given a unique ID number as a substitute for personal information and this will be attached to any results from tests. This will be kept in compliance with the Data Protection Act. This anonymised data will be stored and may be published. Any other personal information will be stored on a password-protected database and only accessible to the Principle Investigator. This will be kept separately from documentation of results, ensuring information is not matched and avoid accidental identification. The NESI Structured Interview will be recorded on a digital device and transcribed; any recorded data will then be destroyed from the digital device. All of the data will be kept for 5 years as per study policies.

8.4 INDEMNITY

Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study.

8.5 SPONSOR

Imperial College Healthcare NHS Trust will act as the main Sponsor for this study.

8.6 AUDITS

The study may be subject to inspection and audit by Imperial College Healthcare NHS Trust under their remit as Sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the Principal Investigator.

10. PUBLICATION POLICY

The results will be included in the final MSc Project and in ethical applications for the secondary phase, where the evaluation will take place. The results will be published in peer reviewed journals, conference papers and research presentations. The anonymity of the participants will be ensured when publishing. If participants wish to receive a summary report of the findings at the end of the study then they may request this.

All publications and presentations relating to the study will be authorised through the Chief Investigator and Academic supervisor. If there are named authors, these will include at least the trial's Chief Investigator, Statistician and Trial Coordinator. Members of the TMG and the Data Monitoring Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

11. REFERENCES

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