ANNUAL TINNITUS RESEARCH REVIEW 2017

British Tinnitus Association

Editors
David Baguley & Nic Wray

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British Tinnitus Association
Unit 5 Acorn Business Park
Woodseats Close
Sheffield
S8 0TB

www.tinnitus.org.uk
info@tinnitus.org.uk
0114 250 9933

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INTRODUCTION

Professor David Baguley

How would we know if the tinnitus research field was thriving? There are a number of indicators that we might observe. This could include increasing numbers of research papers, with studies on many different aspects of tinnitus. One would also seek to find research studies with significant depth, and large numbers of participants, from many different disciplines, whilst evidencing multidisciplinary and international collaborations. New treatments would be subject to rapid assessment with well-designed independent clinical trials. Finally, publication in mainstream and high impact factor scientific journals would evidence a strong and vibrant field. There is no absolute threshold for these and other variables in order for us to consider that tinnitus research is in good health, but there are indications that for each of these factors the situation continues to improve. This is undoubtedly encouraging, though there is considerable distance yet to travel, and sustained effort will be required.

In this edition of the British Tinnitus Association Annual Tinnitus Research Review (ATTR) our spotlight falls upon research published in 2016. Each year the chapter headings and framework of the ATTR will change, to avoid repetition and to draw attention to aspects of tinnitus research that may not be as high profile as others. This year there is careful consideration of developments in devices and technologies, including hearing aids/combination devices, cochlear implants, other treatment technologies, and the use of the internet to deliver tinnitus therapy. Hyperacusis merits a standalone chapter, and the (slow) progress towards drug treatments for tinnitus is described. The ATTR also has interviews with tinnitus researchers, to give insights into how and why tinnitus research is actually undertaken. This year we are fortunate to have been in conversation with Dr James Henry, 2017 winner of the Jerger Career Award in Hearing of the American Academy of Audiology, who has done so much to transform treatment for US military veterans with tinnitus and hyperacusis, and with Susanne Nemholt Rosing, who in 2016 completed a doctoral study on tinnitus and hyperacusis in children and adolescents. Dr Magda Sereda, BTA Head of Research, reviews BTA funded research and the encouraging progress to date.

I warmly thank all the contributors and interviewees for their time and energy, and my co-editor Nic Wray from the BTA, whose cheerful graft and tenacity have been greatly appreciated.

Having edited two editions of the ATTR I have completed my term of office as Editor, and I would like to thank the BTA for that opportunity, which has been a pleasure and a privilege. It does seem to me that the ATTR is a valuable opportunity to enable busy clinicians to keep up to date with research in tinnitus and related fields, but also for us as a community to reflect each year upon recent progress, and where further efforts and resources are needed.

Nottingham, Easter 2017

DR MAGDALENA SEREDA
Senior Research Fellow
British Tinnitus Association
Head of Research,
National Institute for
Health Research (NIHR)
Nottingham Biomedical
Research Centre,
Nottingham, UK

Magdalena is a Senior Research Fellow - British Tinnitus Association Head of Research at the NIHR Nottingham Biomedical Research Centre. Her research focuses on assessing the effectiveness of NHS contracted sound therapy options for tinnitus including hearing aids and combination hearing aids.

Magdalena graduated from Warsaw University in Biology and obtained a PhD in Neuropsychology from the Institute of Experimental Biology, Warsaw. As a Guest Researcher at Humboldt University, Berlin she was researching animal models of tinnitus. In 2007 she started working as a Career Development Fellow at the MRC Institute of Hearing Research in Nottingham to look at objective characterisation of tinnitus using magnetoencephalography.

Over the years Magdalena's research has concentrated on several aspects of the functioning of the auditory system, including cochlear implant technology and tinnitus. She has 16 years' experience of working with people with different hearing disorders including tinnitus sufferers, cochlear implant users and deaf adolescents.

THE BRITISH TINNITUS ASSOCIATION RESEARCH PROGRAMME

Dr Magdalena Sereda

The vision of the British Tinnitus Association (BTA) is "A world where no one suffers from tinnitus" [1], therefore the BTA's research programme concentrates on the areas leading towards achieving that goal. The BTA is currently supporting 14 active research projects involving 21 researchers from 9 institutes across the country, investing over half of its spending in the last year in research [2]. The BTA supported research concentrates around three main areas:

- Understanding tinnitus – with the view to facilitate the development of a cure
- Management – including existing and novel practice and treatment
- Prevention – use of ear protection by young people

Understanding tinnitus

Although research is ongoing, there is currently no pharmacological treatment that has been approved specifically for tinnitus. The route to developing new treatments is complex and involves extensive pre-clinical work before any testing in humans can begin. That includes developing a thorough understanding of the mechanisms involved in tinnitus generation, identifying therapeutic targets, investigating what effects the drug can have on the organism, checking if the drug is safe, estimating a dose for use in people etc. Usually, both in vitro (studies with microorganisms, cells or molecules outside of the body) and in vivo (studies involving living organisms) are needed before the new treatment can be tested in a series of clinical trials.

Dr Martine Hamann from the University of Leicester is currently conducting an early work that is looking at molecular mechanisms of tinnitus and aims to identify novel genetic targets that can be used in the treatment of hearing loss and tinnitus.

Figure 1
Martine Hamann

Dr Hamann is investigating the role of microRNAs (recently discovered small molecules present in animal and human cells) in hearing loss and tinnitus. MicroRNAs play an important role in gene regulation. The first part of her work is concentrating on confirming the role of microRNAs in tinnitus in an animal model. If successful, the next step will be developing a pharmacological treatment that will target levels of these molecules and might lead to alleviation of tinnitus.

Management

Whilst researchers are looking for a cure, there are many different management options that can help reduce the impact of tinnitus on someone experiencing the condition. The BTA is funding research into improving currently available options as well as testing novel treatments and therapies. Other projects in this area are looking at the current clinical practice and potential areas for improvement as well as developing tools for assessing the efficacy of different management options in clinical trials.

In July 2015, the BTA funded a four year Head of Research post for Dr Magdalena Sereda at the then NIHR Nottingham Hearing Biomedical Research Unit (BRU), now part of the NIHR Nottingham Biomedical Research Centre. Dr Sereda's research programme focuses on National Health Service (NHS) contracted sound therapy options (i.e. hearing aids and combination hearing aids) for tinnitus. The programme comprises studies to:

Identify current clinical practice regarding sound therapy for tinnitus;

Define the current state of knowledge and quality of the research evidence behind treatment options with the aim to identify gaps in current knowledge and topics where evidence needs to be provided (scoping and systematic reviews);

Address those gaps by designing and conducting high quality clinical trials, including Randomised Controlled Trials;

Disseminate results to inform and influence clinical practice and guidelines, and to engage the general public.

The projects within the programme include designing and obtaining funding for a UK-wide clinical trial looking at the effectiveness of hearing aids for people with tinnitus and hearing loss and exploring current UK clinical practice around provision of combination hearing aids (amplification and sound generation within one device).

As a member of the steering committee for the British Society of Audiology (BSA) Tinnitus and Hyperacusis Special Interest Group, Dr Sereda is working towards creating professional tinnitus guidelines including guidelines around candidacy and fitting of combination hearing aids. Additional funding to support that work has been secured from the BSA and information about current UK practice is being gathered via a UK-wide survey. Eighty-nine clinicians have already responded and shared their practices and opinions. The next step will be a consensus exercise that will directly inform the guidelines.

A recent collaboration between Dr Sereda and the BTA is focusing on mobile applications (apps) for the management of tinnitus. Currently available tinnitus apps postulate a range of mechanisms by which they might be effective for managing tinnitus including masking, modulation of brain activity, or relaxation. The study will generate the list of apps used by people with tinnitus, and explore and describe the options and management techniques available in each of those apps, their usability, and people's experiences. The results will inform the choice of apps offered by clinicians to people with tinnitus for aiding the management of tinnitus as well as inform future research directions such as the need for effectiveness assessment.

Psychological therapy is one of the tinnitus management options recommended by the Department of Health *Good Practice Guide* [3] Amongst different psychological approaches, therapist led Cognitive Behavioural Therapy (CBT) has good evidence for effectiveness in managing tinnitus distress [4]. Another approach is Mindfulness Behavioural Cognitive Therapy (MBCT), which has been successfully applied to manage depression and chronic pain, but up to now there was no evidence for its effectiveness for tinnitus. MBCT involves teaching meditation techniques – usually in a group format – over a course of eight weeks, paying careful attention to one's physical, emotional and cognitive experiences. Between 2013 and 2015, Dr Laurence McKenna and Dr Liz Marks from University College London Hospitals (UCLH) conducted a study assessing effectiveness of MBCT for tinnitus and compared it to the Relaxation Therapy (current standard treatment). Seventy-five participants took part and the results have shown that both MBCT and Relaxation Therapy resulted in reductions in tinnitus severity, psychological distress, tinnitus loudness, anxiety and depression. However, for MBCT those positive effects lasted much longer (up to 6 months). The results were presented at the 10th International Tinnitus Research Initiative Conference and a research publication describing the results of the study has been submitted to the medical journal *The Lancet*. The long term goal is to adopt MBCT more widely as a treatment for tinnitus.

Following on from that project, Dr McKenna and Dr Marks are continuing their research in this area by looking at how CBT can be used to treat tinnitus-related insomnia. About 70% of people with tinnitus complain of sleep disturbance including getting to sleep or staying asleep [5} {6] and poor sleep may contribute to tinnitus distress. Currently there has been limited research into tinnitus-related insomnia and the most effective management options for it. However, there is evidence that CBT can be effective for insomnia either on its own or co-morbid with other health problems. CBT for insomnia (CBTi) is now part of the NICE guidelines for the management of long term insomnia [7]. The study will assess the effectiveness of CBTi for tinnitus-related insomnia and compare it to the current standard approach of sleep hygiene.
In a BTA-funded PhD project, Lucy Handscomb at the University of Nottingham is assessing a new cognitive model of tinnitus distress and its applications to patient management. Patient reported outcome measures (questionnaires) were used to assess such elements as tinnitus distress, anxiety, coping, insomnia, depression and general wellbeing and fit to the model will be tested. The ultimate goal of the project is to evaluate the interplay between current practice, patient priorities and components of the model to improve patient care. Several aspects of this work looking at properties of different questionnaire measures used in the study and methods of data collection have been published during the last year [8] [9] [10].

Dr Sally Erskine from the Norfolk and Norwich Teaching Hospitals NHS Foundation Trust is exploring the application of Eye Movement Desensitisation and Reprocessing (EMDR) to treat tinnitus. Eye movement therapies have previously been used for treating phantom sensations, such as phantom limb pain (the sensation of pain in an amputated limb) [11] [12]. Tinnitus may be considered a phantom auditory sensation so EMDR is a plausible treatment to test. The study will provide information on feasibility, acceptability and outcomes of EMDR in patients with tinnitus that will inform the development of a larger study looking at effectiveness of this approach.
Dr Sam Lear from Sheffield Children's Hospital is exploring the relationship between tinnitus, hyperacusis and anxiety in children aged 8-16 years. The outcome of this study may help clinicians seeing children with tinnitus and/or hyperacusis to decide whether additional treatment for anxiety may be needed.

Figure 2
James Jackson

A questionnaire study by Dr James Jackson from Leeds Trinity University is investigating the association between personality and individual differences on tinnitus distress. Most people habituate to their tinnitus over time, however, many do not. Understanding the relationship between personality and tinnitus distress may contribute to understanding why some treatments and strategies work for some people, but not others.

Shared Decision Making (SDM) is a process by which clinicians and patients are involved in decisions about their care and treatment. Despite SDM being a principle of healthcare provision highlighted by the NHS mandate [13], it is still not common in tinnitus services. In many cases, the treatments offered are those that the clinician prefers, without taking the patient's preferences and desired outcomes into account. This results in high levels of dissatisfaction with the management options. Dr Helen Pryce from Aston University is currently developing an 'Option Grid' that will provide a tool for clinicians and patients to communicate the choices in a standardised way and facilitate the decision making process. Option Grids are one-page evidence-based summaries of available options, including trade-offs and frequently asked questions [14]. Firstly, the researchers will find out how decisions are made in the clinic. Secondly, they will ask people with tinnitus what they need to know to be able to make decisions about their care. The final step will be designing a randomised controlled trial to check whether the grids work.

Appropriate outcome measures are of major importance in conducting clinical trials. However, there is a considerable variability in outcome measures (usually questionnaires) used in tinnitus research. In 2014 a European research network (TINNET) was funded by the COST programme, with a working group looking at development of standards for outcome measurements in clinical trials. Within that working group, a pan-European initiative called Core Outcome Measures in Tinnitus (COMiT) emerged with the aim to develop a core outcome set to be used in tinnitus trials worldwide. This initiative is led by NIHR Nottingham Hearing BRU. Dr Adele Horobin received funding from the BTA which will allow the incorporation of the patients' voice in agreeing which aspects of tinnitus are important to measure. The study is using a Delphi review - an established method for gaining agreement between different people - and will result in the development of a 'core outcome set' (i.e. a list of things that should always be measured) for tinnitus. So far, patients have contributed to the project by creating plain English definitions and information sheets that will be used throughout the study.

Tinnitus-specific questionnaires are an essential component of tinnitus assessment. They can be used to measure a variety of tinnitus related symptoms and to estimate the effect of different treatments. More than 10 clinical questionnaires exist for use with adults, but there are currently none in existence or appropriate for use with children. The aim of a three-year PhD project at NIHR Nottingham Hearing BRC supervised by Dr Derek Hoare is to create a questionnaire that will reliably measure tinnitus-related quality of life in children. Researchers will be following a careful and tested research approach to define why tinnitus is a problem to children. They will gather perspectives from children who have tinnitus, their parents, and the clinicians who look after them. The project will bring together a multi-disciplinary team with combined expertise in tinnitus, clinical questionnaires, and child health.

Dr James Jackson from Leeds Trinity University conducted a preliminary study looking at the potential of the Cortisol Awakening Response (CAR) as a biomarker of distress in tinnitus sufferers. Cortisol is a stress hormone that regulates the release of sugars into the blood stream. CAR is a well described and consistent phenomenon and any deviation from the usual profile may indicate that the body is under stress. Dr Jackson's study investigated CAR in 30 participants with tinnitus and found that distressed tinnitus sufferers have low cortisol levels, which may be connected to the feelings of lack of control over tinnitus, an inability to relax and emotional distress caused by tinnitus. Currently tinnitus-related distress is measured using subjective measures such as questionnaires. CAR can provide a measure of stress and anxiety and offers a potential way to objectively measure tinnitus and the effectiveness of any tinnitus interventions. The results of the study were presented at the BTA Conference in September 2016. A larger-scale study is now needed to test whether effectiveness of tinnitus treatments can be measured using CAR.

Prevention

It has been well documented that exposure to loud noise is associated with a greater risk of tinnitus and hearing problems [15] [16]. Despite that, the majority of young people do not do anything to protect their hearing [17] [18]. The BTA's prevention campaign "Plug'em" aims to encourage wearing earplugs at gigs, festivals, clubs and other places where one can be exposed to high levels of noise [11]. Dr Abby Hunter from the then NIHR Nottingham Hearing BRU, now the NIHR Nottingham Biomedical Research Centre, conducted a series of focus groups and interviews with young adults to explore their attitudes to loud music, knowledge, perception of risk, and protective behaviours. The study found that people display different behaviours despite recognising that their hearing problems have been caused by noise exposure. Whilst some people had difficulty coping with their tinnitus and avoided loud places, others would carry on as normal and did not protect their ears. Only some made a positive change and decided to wear earplugs in noisy places. Dr Hunter postulated that the different behaviours can be linked to different personality types. The results of the study will aid and inform prevention campaigns and hearing education programmes that aim to raise awareness, but will also be used to motivate young adults to take preventive measures. Findings will help to design and tailor online/app-based material to address all the above issues and ultimately reduce the incidence of tinnitus and hearing loss in this population.

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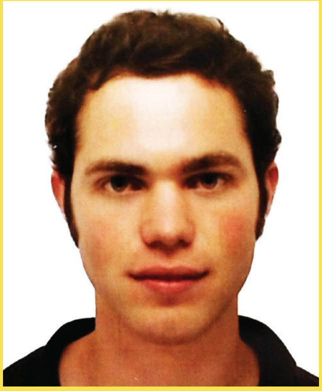

DR WILLIAM SEDLEY
Training Fellow
Institute of Neuroscience,
Newcastle University

William Sedley is an academic clinical lecturer in neurology based in Newcastle upon Tyne, and divides his time equally between conducting research in human volunteers into tinnitus and related aspects of perception, and practicing as a trainee neurologist. He graduated from Nottingham Medical School in 2007, subsequently joining the research group of Prof. Tim Griffiths, in which he still works today. His research has been funded by the National Institute of Health Research, as part of an integrated academic training pathway for doctors, and by the Medical Research Council for his PhD which he completed in 2015.

THE NEUROSCIENCE OF TINNITUS: FINDING THE NEEDLE IN THE HAYSTACK

Dr William Sedley

Tinnitus tends to occur in people who have a degree of hearing loss, which itself is associated with a wide range of changes in the structure, chemistry and function of many parts of the brain. Many studies on tinnitus to date have compared groups of patients or animals with tinnitus to controls unmatched for hearing levels. These have shown striking differences, but cannot demonstrate which of these simply relate to hearing loss and which, if any, are specific to tinnitus. Fortunately, this issue is now widely recognised, with positive steps being taken to separate correlates of tinnitus from those of hearing loss or other confounds.

This summary of new research findings in 2016 begins with those that seem to contradict the results of previous less carefully controlled studies. Next, it highlights key advances in our ability to study tinnitus, on account of greater understanding of its relationship with hearing loss and improved ways of determining whether animals are experiencing tinnitus. Finally, it discusses advances in understanding of how tinnitus relates to changes in the auditory (hearing) pathway and wider parts of the brain.

Two steps forward, one step back

A popular theory of tinnitus is that hearing loss leads to reduced input to parts of the brain's hearing pathway, which causes the gain (or 'volume dial') to be turned up to compensate. The gain is also turned up on spontaneous firing of brain cells, leading to increased firing rates that result in the perception of sound. Previous work has shown that animals with tinnitus induced by hearing loss do indeed show such increases in nerve firing. However, hearing loss itself is associated with such changes. A new study by Longenecker and Galazyuk [1] addressed this issue by causing standardised noise damage in sixteen mice, and determining which ones did and did not show evidence of tinnitus. The researchers made the additional advancements of making recordings from the auditory midbrain (an early hearing centre) with the animals awake, and therefore presumably experiencing tinnitus, rather than anaesthetised. They found that all the animals showed increased nerve firing rates, irrespective of tinnitus, and also that another pattern of altered nerve firing previously attributed to tinnitus, called 'bursting', occurred in some animals that did not show evidence of tinnitus, and failed to occur in some animals that did. While this was just one relatively small study, and requires further corroboration, it does suggest that these processes alone are unlikely to be the principal basis for tinnitus in the brain.

In humans, it is rarely possible to measure spontaneous electrical brain activity except at a high level in the brain – the cerebral cortex. Synchronised rhythmic firing of very large numbers of brain cells produces oscillations – or 'brainwaves' – that can be detected using electroencephalography (EEG). However, there are other strong sources of electrical activity on the scalp, including movements of the muscles and eyes. The last decade has seen many studies reporting abnormal oscillations at the scalp over the auditory (hearing) parts of the brain, and even most of the rest of the scalp, which in some studies have been very dramatic. These changes have appeared to be able to distinguish tinnitus patients from controls, and to correlate with tinnitus severity and other markers. This has led to high hopes for the use of EEG as both a diagnostic test for tinnitus, and as a biomarker of response to treatment. However, a recent study by Pierzycki and colleagues [2] has cast doubt over the usefulness of EEG in this regard. This study featured a larger sample of tinnitus patients than most previous similar studies, and tested each participant on two separate occasions. The results showed good correspondence between each participant's recordings from the two sessions (suggesting that the results were reliable), but no significant relationship between any type of recorded activity and any aspect of the tinnitus experience. The major limitations of the study were that it did not feature a non-tinnitus control group, and that it only looked at average electrical activity over the whole scalp, rather than anything specific to a particular area or brain location. However, at present it seems doubtful that the very striking differences in electrical activity at the scalp previously attributed to tinnitus are actually meaningful. Future similar studies will need to use much more subtle, nuanced measures, as well as demonstrating reliability across multiple studies.

For over a decade there has been substantial interest in whether changes in the physical structure of the brain (e.g. specific areas of loss or gain of brain cells) might affect the risk of developing tinnitus, or occur as consequences of longstanding tinnitus. However, perhaps partly due to a varied range of research methods and tinnitus patient characteristics, the findings of different studies have been starkly contradictory of each other, without any consistent findings emerging. Sadly, this year has been no different, with one large study showing localised brain changes in association with duration of tinnitus [3] but another large study [4] showing striking widespread changes on account of age but no changes attributable to tinnitus once age had been accounted for.

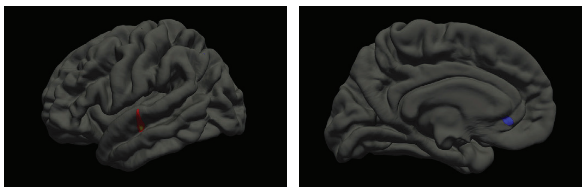

Figure 1
Areas of altered thickness or the brain (red = increased, blue = decreased) reported to occur with increasing duration of tinnitus in the left hemisphere of the brain [3]

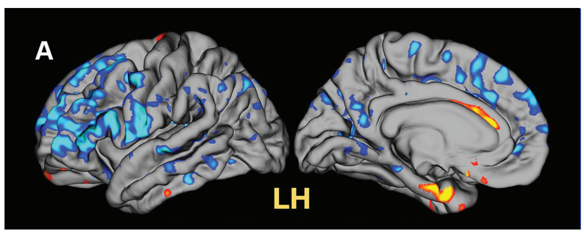

Figure 2
Areas of altered thickness of the brain occurring with age, with layout and colour scales as for previous figure. Once age was accounted for, no changes attributable to tinnitus duration were observed.[4]

Yet another large study, by Allan and colleagues [5], comparing tinnitus patients to controls carefully matched for age and hearing found only very small differences, most of which were contradictory to results of previous studies.

Hearing loss

Recent studies have shown that when two groups of age-matched volunteers have been compared – one with tinnitus and normal audiograms (standard hearing tests), and the other with no known tinnitus or hearing problem – the tinnitus group have shown evidence of ‘hidden’ hearing loss. This has been demonstrated in the form of reduced electrical responses to sound stimulation generated by the auditory nerve [6] [7]. This hidden hearing loss was thought to underlie tinnitus. New findings have revealed that the situation is more complicated than this. Two similar studies in the past year have focused on volunteers with tinnitus and normal audiograms, with one checking that even the very highest frequencies (normally omitted from testing) were matched between groups. One of these studies, by Konadath and colleagues [8], found that electrical responses from both the auditory nerve and midbrain were reduced in the tinnitus group, therefore showing hidden hearing loss but not the compensatory increases in central gain believed to underlie tinnitus generation. The other study, by Guest and colleagues [9], found no differences in auditory nerve or brain responses between groups, though it did find a greater history of previous noise exposure in the tinnitus volunteers. Rather than recruit groups with and without tinnitus, and search for differences between them, a new study by Gilles and colleagues [10] took the different approach of recruiting a group of young adults with symptoms of hearing loss due to recreational noise exposure, and then grouping the volunteers according to whether or not they experienced ongoing tinnitus. They tested various aspects of their hearing, and could detect no difference between the two groups in standard hearing tests, including the very high frequencies, nor other clinical measures including electrical auditory nerve responses. Therefore, the degree of hearing loss of any of these types did not seem to be the deciding factor in who developed tinnitus. What the study did find was that the tinnitus group were slightly, but significantly, worse at correctly hearing speech in the presence of background noise.

Another approach being taken is to consider two major types of nerve fibres connecting the cochlea to the brain. The first type are the low-threshold fibres, which are activated by even quiet sounds and form the basis of standard audiogram results. The second type are high threshold fibres, which are activated only by louder sounds. Because loud sounds are infrequent and short-lived in nature, these fibres are not adapted for long periods of activation and are therefore vulnerable to damage or death if activated for too long. A study by Paul and colleagues [11] has measured responses in tinnitus patients and controls with matched audiograms, and used computer modelling of the results to show that tinnitus patients tend to have relatively greater damage to these high threshold auditory nerve fibres. In summary, there have been significant advances in our understanding of the relationship between hearing loss and tinnitus, but a consistent pattern has yet to emerge.

Animal models

Animal tinnitus studies allow very detailed assessments of structure or function in any part of the brain. However, to date they have been hampered by two main limitations in actually being able to attribute any observed changes to tinnitus itself: the difficulty in assessing whether an animal is experiencing tinnitus, and the tendency to compare groups of animals with tinnitus plus hearing damage to control groups with undamaged hearing. However, recent improvements in experimental techniques have made major progress towards addressing these issues. Some studies have focused on improving conditioned behaviour methods, where animals are taught to perform certain tasks either in the presence of sound or quiet [12} {13]. Others have used the automatic startle response elicited by unexpected sounds, which does not require lengthy prior training of the animals. Previous versions of this method had been confounded by changes in this response on account of hearing loss itself and its other consequences such as hyperacusis, and deficits in processing the precise timing of sounds. Now, a group of researchers has carefully disentangled these separate effects, and shown that there are aspects of the startle response changes that appear to be uniquely associated with tinnitus as opposed to confounding factors [14]. Separately, the research group of Jeremy Turner, who originally developed the startle response method, has also used a refined form, examining animals shortly before tinnitus onset, soon after, and 12 months later [15]. They found that long or very intense periods of noise damage were more likely to cause hyperacusis, and longer or milder periods of noise overexposure were more likely to cause tinnitus. While these findings are in themselves interesting and useful for understanding tinnitus, the main gains should accumulate over time as these refined methods are adopted in other studies of brain changes in tinnitus.

One new approach being facilitated by refined animal models is to focus on genetics rather than brain structure or activity. Yu and colleagues [16] studied mice with and without a mutation in a gene called GLAST, which regulates the balance of excitation and inhibition. They then applied salicylate, a drug known to cause tinnitus in overdose, and found greater behavioural evidence of tinnitus in mice with the mutation. It remains to be seen how applicable these findings are to noise-induced tinnitus, and to humans, but this potentially opens a new avenue to investigate mechanisms and treatments for tinnitus.

Auditory (hearing) pathway and beyond

A good example of a recent animal study to carefully distinguish between equivalently hearing damaged animals with and without evidence of tinnitus was one by Wu and colleagues [17]. In a study of guinea pigs with induced hearing loss, they found increased rates of nerve firing and synchrony in the first auditory processing centre in the brain – the dorsal cochlear nucleus – in the tinnitus animals over and above controls. While such changes have also observed with hearing loss irrespective of the presence of tinnitus, this evidence strengthens the case for them forming at least part of the basis of tinnitus. Further up the auditory pathway in the auditory midbrain, rather than trying to correlate spontaneous brain activity with the presence of tinnitus, Smit and colleagues applied rhythmic electrical stimulation to animals that had shown behavioural evidence of tinnitus [18].

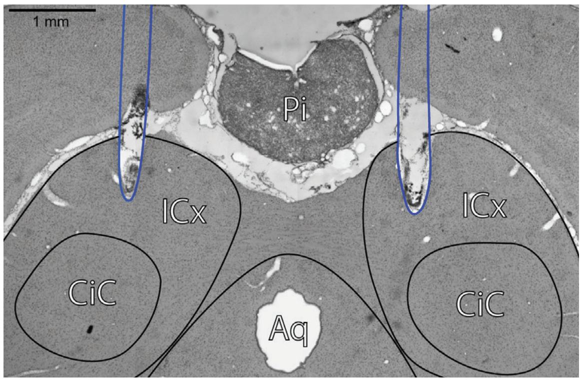

Figure 3
Magnified view (note scale bar in top left) of rodent midbrain (target area = inferior colliculus, labelled ICx), showing the placement of the electrodes (blue) used for delivering deep brain stimulation to treat tinnitus. [18]

They found that this treatment – called deep brain stimulation (DBS), which applied elsewhere in the brain already has a role in treating disorders such as certain cases of Parkinson's disease – eliminated evidence of tinnitus. Interestingly, the same group of researchers [19] looked at patients with tinnitus undergoing DBS for coexisting Parkinson's disease.

Although the areas targeted were all outside of the auditory system, they found that DBS treatment to a particular area called the subthalamic nucleus (STN) significantly reduced tinnitus loudness in certain individuals.

This highlights the importance of additional brain circuitry in tinnitus, beyond the auditory pathway or areas interacting with it. Another study to examine the influence of auditory and wider brain networks on tinnitus was performed by Vanneste and colleagues [20]. In this, they studied EEG 'brainwave' signals recorded from a large group of tinnitus patients while they rested. They categorised patients depending on their level of hearing loss, and found two key differences in brain activity: patients with less hearing loss showed more on-going activity in part of the auditory cortex, while patients with more hearing loss had more on-going activity in a memory centre called the parahippocampal cortex.

The researchers interpreted this as evidence of the tinnitus signal being generated differently - in the hearing system, or retrieved from memory – depending on the degree of hearing loss. However, other interpretations are possible. Although a control group was included, these non-tinnitus volunteers had no known hearing loss, so it remains to be seen whether similar activity patterns are seen in association with different levels of hearing impairment in patients without tinnitus. Perhaps in keeping with this result, the results of another study by Hong and colleagues [21], has suggested that abnormal generation of internal predictions, which are fundamental to normal perception, may be involved in tinnitus. This focused on the brain's 'P300' response, which occurs following unexpected events such as sounds, and found it to be smaller in patients with tinnitus, and to show an altered pattern of communication between the brain centres that generate this response. Collectively, these findings suggest that the brain mechanisms responsible for tinnitus may include both generators in the auditory pathway, and wider networks that modulate this activity and may even make the difference between whether it gets perceived as sound or not. Further research should aim to build upon these findings by generating more specific hypotheses, and running studies that support, refute or refine these.

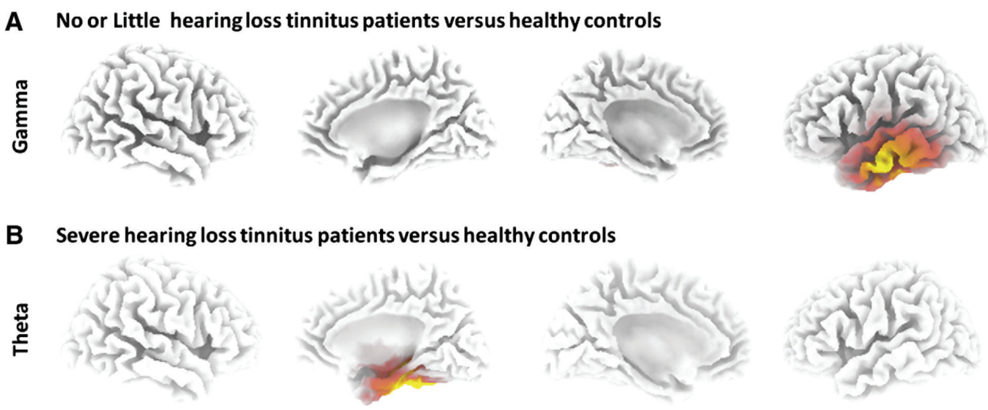

Figure 4
Changes in resting-state 'brainwaves', compared to normal hearing non-tinnitus controls, in tinnitus with relatively little hearing loss (top row) and tinnitus with severe hearing loss (bottom row). Coloured areas indicate increased strength of brainwaves in the tinnitus group.[20]

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DR GRANT D SEARCHFIELD
Associate Professor/Director
The Hearing and Tinnitus Clinic, University of Auckland

Associate Professor Grant D Searchfield is Deputy Director of the Eisdell Moore Centre for Hearing and Tinnitus and Director of the Hearing and Tinnitus Clinic at the University of Auckland, New Zealand. He is a member of the Scientific Advisory Committee of the American Tinnitus Association.

HEARING AIDS AND COMBINATION DEVICES

Dr Grant D Searchfield

Hearing aids have been used to treat tinnitus since the 1940's. Hearing aids combined with sound generators for masking became available in the early 1980's. Because tinnitus is often accompanied by hearing loss, engineers and researchers have tried to address both problems simultaneously. The availability of digital signal processing and hearing aid compatibility with smartphones has seen new sound therapy ideas emerge. Sound therapy is the use of sound to assist tinnitus. While different sound therapies have been made possible by new hearing aid technology often the evidence for effectiveness is weak. A scan of the literature published in 2016 was undertaken using the terms "tinnitus" and "hearing aids" [or] "combination" [or] "instruments".

Commercially available devices

Aazh and colleagues [1] undertook a survey of patients' views of the effectiveness of the interventions provided by the Tinnitus and Hyperacusis Therapy Clinic at the Royal Surrey County Hospital. The survey found that 64% of respondents found hearing aids were useful or very useful. These patients also received counselling making interpretation of the relative contribution of treatment components difficult. Several small studies from Brazil looked at the benefits of hearing aids [2][3] and combination devices [4][5][6]. The study designs didn't allow for strong conclusions to be made, but the authors believed the results were consistent with the devices reducing tinnitus.

Another small-scale study, investigating the feasibility of evaluating a combination device, was undertaken in the UK [7]. The trial aids were set with 4 programmes:

- Amplification
- Amplification and masking noise (with manual volume control)
- Amplification and masking noise (with automatic adjustment)
- Amplification and ocean sound (with manual volume control).

Although the study only had eight participants, it did make some interesting observations. Preferences for sound varied across environments, and while the noise was the most effective masker, the ocean sound provided distraction and/or was relaxing. The authors suggest that flexibility is needed in fitting these devices to suit each individual's preference.

A larger study that demonstrated the benefits of hearing aids for tinnitus also provided interesting insight into the potential mechanisms of effect [8]. The effects of hearing aids on a group with tinnitus and hearing loss were compared to a group with just hearing loss. The results showed improved sleep and hearing with reduced tinnitus following hearing aid use. Interestingly, concentration (using a reading span test) also improved in tinnitus patients after hearing aid use. The authors concluded:

"...hearing aid fitting should be a central part of tinnitus treatment in patients with both tinnitus and hearing loss" (p 150).

Notched environmental sound

Tailor-made notched music is a treatment proposed to suppress tonal tinnitus by a lateral inhibition mechanism [9]. A filter is applied to music of the listener's choice at their tinnitus pitch-matched frequency (the notch). The method has been used with encouraging results. A modification of this concept was trialled in which notched filtering of environmental sound was used instead of music [10]. A group of 10 participants trialled the notched environmental sound compared to 10 controls using standard amplification. The group receiving notched amplification showed greater improvement in the Tinnitus Handicap Questionnaire (THQ) [11] over three weeks than normal amplification. The concept is an interesting one that requires further evaluation in larger numbers of participants over a greater time period, and with consideration of effects of notching on speech perception.

Spatial masking

The use of sound to partially or fully mask (cover) tinnitus has focused on the appropriate level and spectrum of sound to interfere with tinnitus. Another aspect of masking in real-world situations is where the sound is located. A masker that has the same location as a target sound is more effective than if they are separated in space. This was the topic of an iterative series of small studies [12]. The studies explored whether masking sound localised (using interaural timing and intensity changes and Head Related Transfer Function [HRTF]) to the same location as a person's tinnitus (eg "right-side towards front of head") would be more beneficial than conventional masking. The first study used headphones then the method was applied using hearing aids. The results indicated variation in preferences but across all three studies the modified spatial masking was preferred. As with many of the studies reviewed here, larger sample sizes and longer treatment times would help clarify effectiveness.

Figure 1
Hearing aid
(picture courtesy GN ReSound UK)

Nature sounds

The convergence of hearing aid and smartphone technology now enables hearing aid users to stream sound from their personal music library to their hearing aids via Bluetooth connections. Most hearing aid manufacturers have developed apps (mobile applications) for this purpose and there are various websites where sounds for tinnitus treatment can be accessed.

Barozzi and colleagues [13] hypothesised that nature sounds would evoke more positive emotional responses than noise and this would improve the response to treatment. A multisite trial was undertaken comparing a group (17 participants) using combination aids with conventional broadband noise to a group (19 participants) using similar hearing aids but streaming

Figure 2
Combination hearing aid used in recent study by Sereda *et al* [7]

user-selected nature sounds. Significant improvements in the Tinnitus Handicap Inventory (THI) [14] were achieved at three and six months compared to baseline, but there was no distinct advantage of one sound type over another. The preferred nature sounds were some form of running water. It was not explored if certain sounds (e.g. with relaxing qualities) may be more beneficial for some persons while other sounds (e.g. more effective in masking such as broadband noise) might benefit others more.

Music

Music has been used in various forms as a therapeutic tool for tinnitus. Some of these therapies modify the music in order to compensate for hearing loss, so as to ensure audibility of the treatment sound. The Heidelberg model is a music therapy; the treatment does not use passive exposure to sound: instead a music therapist guides vocal exercises in response to music and relaxation exercises over five consecutive days [15]. The music is not adjusted for audibility (music is live, played on a piano). This raised the question as to whether persons with hearing loss would benefit more from the therapy if they wore hearing aids? Three groups of 40 participants were compared, one with hearing loss and hearing aids, one with hearing loss and no aids, and a normal hearing group. The normal hearing group and the group with hearing aids showed greater improvement in Tinnitus Questionnaire (TQ) [16] scores than the group with hearing loss but no aids. For full potential of the treatment to be met, patients with hearing loss should be using hearing aids.

Conclusions

The research published in 2016 demonstrates the value of hearing aids across different treatment settings. It also identifies that many of these novel treatments are at developmental stages. Digital signal processing has facilitated many novel approaches for sound therapy using hearing aids and combination instruments. Although the majority of studies use small samples, and so provide low levels of evidence, they are necessary to provide proof of concept and feasibility for future randomised controlled trials (RCTs). RCTs for hearing aids are expensive and when the developments have commercial potential the onus is often on companies, as opposed to government and not-for-profit organisations, to fund trials. The research also hints towards the very individual nature of sound therapy and the different mechanisms (masking, relaxation and cognitive benefits) that different sound types may have. My “take home” message from reviewing 2016’s publications on hearing aids and combination devices for tinnitus is that we need to carefully consider each patient’s cognitive, emotional and perceptual needs in selecting sound therapy.

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Conflict of interest. Grant Searchfield receives research funding from, and has commercial interest with, hearing aid manufacturers. Some of that research is described in this article. He is clinical director of Tinnitus Tunes a subscription-based tinnitus treatment website.

COCHLEAR IMPLANTS AND TINNITUS

Dr Robert H. Pierzycki and Dr Pádraig T. Kitterick

Historically, the primary use of the cochlear implant (CI) has been to restore access to sound so that a person with profound hearing loss may understand spoken language [1]. Early candidates for implantation therefore had little or no access to hearing [2]. The technology itself, surgical techniques, and rehabilitation strategies have now advanced to the point that it can provide benefit even to patients with less severe hearing losses [3]. As a result, the criteria for candidacy have changed and patients with a far greater level of hearing than ever before are now eligible to receive a CI [4].

Despite this expansion in the population of patients who are eligible to receive a CI, provision is still focused on improving speech understanding. A recent survey suggested that 85% of countries still define eligible patients in terms of their capacity to understand spoken words or sentences [5]. In the United Kingdom, eligible patients are defined not only in terms of their audiometric thresholds but also in terms of their speech perception abilities [6]. This approach reflects a continued focus on improving speech perception, for which cochlear implantation has been shown to be effective in both children and adults [7].

As the numbers of implanted patients has increased globally, knowledge of the impact of cochlear implantation on patients' health and well-being has also increased. One effect of note is the capacity of cochlear implantation to reduce the percept of tinnitus in some patients [8]. As a large proportion of implant recipients experience tinnitus before implantation [9], studies have noted that the proportion of patients with tinnitus reduces substantially following implantation [10]. Moving towards providing CIs to patients primarily for the alleviation of tinnitus rather than to improve speech perception requires a greater understanding of:

(a) the specific domains of tinnitus-related burden that implantation is effective (or not effective) at addressing;

(b) the type of electrical stimulation that maximises the size of the benefit; and

(c) the patient groups that are most likely to benefit.

DR PÁDRAIG T KITTERICK
Associate Professor
University of Nottingham/ NIHR Nottingham Biomedical Research Centre

Pádraig is an Associate Professor at the University of Nottingham and part of the NIHR Nottingham Biomedical Research Centre, where he leads research on severe and profound hearing loss, including cochlear implantation.

Pádraig graduated from the Conservatory of Music and Drama in Dublin where he completed a Bachelor in Music Performance. He subsequently received a Fellowship of Trinity College London in Piano. He completed an MSc in Music Technology and gained a PhD in Psychology at the University of York by examining the difficulties that older adults experience with understanding speech in noisy environments. Pádraig then held a series of post-doctoral research fellowships carrying out a programme of research on spatial listening skills in users of hearing aids and cochlear implants.

Pádraig came to Nottingham in 2012 as a senior research fellow and established a new research group focusing on evaluating the effectiveness of cochlear implantation in novel patient populations.

Here we summarise a selection of the very latest research evidence on these three topics.

What aspects of tinnitus-related burden does CI alleviate?

Tinnitus imposes a complex burden on those who suffer from it. Persistent tinnitus can impair concentration and make it impossible to relax, and it is often associated with anxiety, depression and disrupted sleep [11][12]. Suppression of tinnitus primarily occurs when CIs are switched on and this effect ceases soon after CIs are switched off [13]. Any positive effects of CI use may therefore be limited to alleviating symptoms that are present when CIs are active, such as making tinnitus less persistent and distressing. Conversely, symptoms that are present when the implant is switched off at night, such as insomnia, may not be alleviated. Patients and clinicians have identified tinnitus-related insomnia as one of the top ten priorities for further research [14] and therefore our own group recently assessed sleep difficulties among CI users [15]. The study used data from the UK Biobank, a population-based cohort of over 500,000 adults [16], and compared CI users to a control group. The control group represented individuals who had the potential to be candidates for cochlear implantation based on their Biobank data on speech perception and hearing aid use. The prevalence of tinnitus was similar (approximately 50%) among both the 194 CI users and the 211 potential candidates. Whilst this may appear counterintuitive if one assumes that cochlear implantation suppresses tinnitus, it is compatible with the fact that it does so primarily when it is switched on and not all the time [17]. This fact was confirmed by the data as tinnitus was found to be less persistent among CI users with only 46% reporting frequent tinnitus compared to 72% of candidates. Encouragingly, this lower persistence was associated with lower tinnitus distress. However, more than 75% of individuals reported usually experiencing sleep difficulties, and this large proportion was similar in both groups. Therefore, although CI use can make tinnitus less persistent and distressing, it does not target all aspects of tinnitus burden with equal effectiveness and may not be a suitable intervention where the primary indication is to alleviate tinnitus-related insomnia. Those receiving implants for other reasons may still require interventions for insomnia despite benefitting from electrical stimulation during the day.

DR ROBERT H PIERZYCKI
Research Fellow
University of Nottingham/ NIHR Nottingham Biomedical Research Centre

Robert Pierzycki is a Research Fellow at the NIHR Nottingham Biomedical Research Centre, where he is currently leading research evaluating the burden of tinnitus after cochlear implantation.

Robert graduated from Adam Mickiewicz University (Poland) with MSc in Physics. He joined the Institute of Sound and Vibration Research as a Marie Curie Fellow and in 2007 obtained PhD from the University of Southampton on “Micromechanical Modelling of the Cochlea.” He then worked at the MRC Institute of Hearing Research in Nottingham as a Career Development Fellow investigating masking phenomena in cochlear implant hearing, and moved to Nottingham in 2012 to co-ordinate a clinical trial of a novel therapy for tinnitus.

Robert's research expertise is in tinnitus and cochlear implantation. His research focuses on the effect of implantation on tinnitus and the tinnitus-related burden post-implantation to develop appropriate tinnitus management strategies for the profoundly deaf.

Figure 1
Cochlear implant unit in use
(image courtesy of Wikimedia Commons)

What patterns of electrical stimulation could be optimal for tinnitus?

Reported levels of tinnitus suppression from CI stimulation vary widely, with a total suppression occurring in only 8-45% of patients [10]. Previous studies have suggested that the optimal parameters for tinnitus suppression are highly individual [18], and may not be optimal for speech perception [19]. Therefore, it is important to understand how electrical stimulation should be delivered to maximise tinnitus suppression without compromising the ability to understand speech, which remains the primary outcome of interest in most implanted patients [21].

Arts and colleagues [21] proposed a customised CI processor capable of providing a looped electric stimulation that does not encode environmental sounds but that can be optimised for tinnitus suppression. Ten patients with hearing loss in only one ear (single-sided deafness, SSD) and ipsilateral tinnitus enrolled into a carefully designed prospective, single-centre, crossover Randomised Controlled Trial (RCT) (NTR3374) [22]. Each patient underwent implantation and standard CI rehabilitation for two months to stabilise loudness perceptions with electric stimulation. Standard CI stimulation was subsequently deactivated and a series of tuning procedures were used to identify the most effective and comfortable electric stimulation pattern for tinnitus suppression. Participants were then randomised to either use the standard stimulation or the optimal tinnitus-alleviating stimulation for three months after which they crossed over to use the other intervention for another three months. After this six-month period, participants used their preferred stimulation method during a three-month follow-up and the results from this follow-up period have now been published [23].

Visual analogue scales and two standard questionnaires, the Tinnitus Handicap Inventory (THI) [24] and Tinnitus Questionnaire (TQ) [25], were used to assess the effect of stimulation on the quality of tinnitus and related burden. Changes in tinnitus loudness and pitch were also assessed by comparing tinnitus to acoustic stimuli presented to the contralateral ear. Although these outcome measures showed a statistically-significant reduction in tinnitus after the follow-up compared to baseline, no difference was observed between the tinnitus-alleviating and standard stimulation patterns. Changes in depression were also monitored using the Beck's Depression Inventory [26], and in the quality of life using the Health Utilities Index Mark III [27]. Neither of these outcomes differed significantly from baseline at follow-up, or between the stimulation methods. Thus, these results suggest that optimised electrical stimulation for tinnitus suppression is not necessarily a prerequisite for the alleviation of tinnitus and related symptoms.

Whilst tinnitus-specific stimulation methods hold great potential for maximising the suppression of the tinnitus percept, it would still be important to question whether a custom stimulation prescription would be feasible to deploy in clinical practice and would be acceptable to patients. In agreement with previous studies [18][19], the present RCT found that optimal stimulation for tinnitus suppression is highly individual [23]. Although the authors argue that their tinnitus-alleviating stimulation patterns are simplified compared to standard speech-based stimulation, they still needed to be tuned (and in some cases re-tuned) to achieve an optimal effect on tinnitus [21][23]. However, whilst only one out of the ten participants chose the tinnitus-alleviation stimulation after the crossover period, six participants did request it to be implemented in their implant so that they could use it on an as-needed basis [23]. Future assessments of the effectiveness of tinnitus-specific stimulation methods may therefore need to account for the fact that not all implanted patients may need tinnitus relief all the time, or may not always be willing to trade off access to sounds in their environment in order for their tinnitus to be suppressed.

What patient groups could benefit from CI?

Systematic reviews have identified a lack of high-quality clinical studies including RCTs of cochlear implantation in traditional candidates with severe or profound hearing loss [7]. Therefore, it is notable that a recent RCT compared the effects of implantation in both ears (bilateral) with implantation in just one ear (unilateral) in 38 patients with bilateral severe sensorineural hearing loss [28]. Because the primary aim was to compare speech perception outcomes in the two groups, not all patients had tinnitus pre-operatively. Seven patients with tinnitus were implanted unilaterally and nine patients were implanted bilaterally. The presence of tinnitus was defined as a non-zero score on either the THI or the TQ. No significant difference in THI scores was observed between the two groups following implantation, although the authors noted a significant change within each group individually. Of the 16 patients who had tinnitus prior to implantation, four (27%) were judged to have had total tinnitus suppression. However, tinnitus was induced in a similar proportion of patients who did not have tinnitus before implantation (six of 22 patients, 27%), which varied in severity from slight to moderate post-operatively. Five of these six patients with newly-induced tinnitus were in the bilateral group, echoing the findings of a previous RCT that observed negative tinnitus effects following bilateral implantation [29]. This new trial highlights the problems inherent with assessing the effect of implantation on tinnitus when it is not the primary purpose of the trial and reinforces the need for controlled trials of cochlear implantation that are designed primarily to assess tinnitus-related effects. The current evidence mostly confirms that there is large variability in the effect that implantation has on tinnitus, including both positive and negative effects.

If cochlear implantation was effective in alleviating tinnitus, eligibility could also potentially be expanded to patient groups other than those with bilateral severe-profound losses. A growing field of research over recent years has been the effects of cochlear implantation in patients with SSD. Even the earliest studies in this area focused on the potential for implantation to alleviate tinnitus [30] and only later assessed benefits to hearing [31]. A systematic review published in 2016 identified seven studies that have assessed tinnitus outcomes following implantation in SSD patients and noted that five found statistically-significant positive effects on tinnitus [32]. However, like previous systematic reviews in this area [33][34], the authors noted heterogeneity in the choice of outcome measures and the absence of high-quality controlled trials. Very little is also known about the longer-term outcomes in SSD patients, including benefits to tinnitus. An important study published during 2016 was therefore one that reported long-term outcomes for a cohort of 23 SSD patients who had been implanted for between three and ten years [35]. The patients had originally been identified as those with a unilateral profound sensorineural hearing loss and incapacitating tinnitus in one ear and either normal hearing (SSD group) or a mild-moderate hearing loss (asymmetric group) in the other ear. Tinnitus outcomes measured using the TQ had stabilised only three months after implantation. No statistically-significant change had occurred over the longer term with benefits still apparent up to 10 years later. Implantation in these patients also had positive effects on speech perception and binaural hearing, but notably tinnitus was considered the most important benefit by 10 of the 12 SSD patients. This result suggests that it may be more relevant to assess tinnitus burden rather than hearing abilities in this patient group when considering candidacy for cochlear implantation.

Conclusions

While cochlear implantation is currently provided primarily for the purposes of improving speech perception, there is a growing body of evidence that it can have positive effects on tinnitus in some patients. Ongoing trials [36] and numerous other ongoing studies assessing the effects of implantation on tinnitus (see http://www.clinicaltrials.gov for NCT02794623, NCT02204618, NCT02532972, NCT02259192, NCT02966366, NCT03026829) highlight the rapid pace at which evidence in this field continues to grow. However, an enduring challenge is to develop criteria that can reliably distinguish patients who are likely to experience tinnitus benefit from those that are not [37]. This task is particularly challenging for tinnitus given that those who may benefit have a far wider range of hearing abilities than traditional candidates for cochlear implantation and the multi-dimensional nature of the burden imposed by tinnitus.

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I HAVE BEEN EXTREMELY FORTUNATE: Dr James Henry talks to Nic Wray

DR JAMES HENRY
Research Professor
National Center for Rehabilitative Auditory Research

James Henry, PhD. is certified and licensed audiologist with a doctorate in Behavioral Neuroscience. He is employed at the National Center for Rehabilitative Auditory Research (NCRAR) located at the VA Portland Health Care System. He is also Research Professor in the Department of Otolaryngology – Head & Neck Surgery at Oregon Health & Science University. For the past 23 years he has devoted his career to tinnitus research. He has received funding for 25 grants to study various aspects of tinnitus clinical management. His overall goal is to develop and validate clinical methodology for effectively helping individuals who are afflicted with bothersome tinnitus.

What made you first interested in tinnitus? How did your research career develop to where it is now?
I became interested in pursuing a career in Audiology because of my deaf daughter. When she was 5 years old I returned to school to earn an M.S. in Audiology. Following school I was hired as a research audiologist at the Veterans Affairs hospital in Portland, Oregon where I discovered an avid interest in research. I spent the next 6 years in the Behavioral Neuroscience doctoral program at Oregon Health & Science University (OHSU). My OHSU research lab was directed by Dr Jack Vernon, and my research advisor was Dr Mary Meikle. They were both pioneers in the field of tinnitus and I had the great opportunity to learn from them. My doctoral dissertation focused on measurement of tinnitus, which cemented my interest in doing tinnitus research as a career. I have been doing it ever since.

My first funded grant was a pilot study to perform computer-automated tinnitus measurement. I have continued that work to the present. I also became interested in Tinnitus Retraining Therapy (TRT) and attended Dr Jastreboff's TRT training course in 1997. I received a grant in 1999 to compare outcomes between TRT and Tinnitus Masking (Dr Vernon's method) and that study led to two other studies evaluating TRT. My combined experiences led to the development of Progressive Tinnitus Management (PTM), which is the method we have focused on for about the last 10 years.

What research are you currently involved in?
I would have to say that further refinement and expansion of PTM is my highest priority. What has always driven my research is the desire to improve clinical services for people who suffer from tinnitus. Until a cure is discovered, the best we can do is to mitigate effects of tinnitus and help people live normal lives in spite of their unremitting tinnitus. PTM is a stepped-care program of clinical management, and the intervention levels focus on teaching self-help skills to enable people to know what to do whenever their tinnitus is bothersome.

We have adapted PTM to provide the self-help education over the telephone. We recently completed a randomised controlled trial (RCT) to evaluate “Tele-PTM” and observed very positive outcomes. This demonstrated the ability to provide tinnitus services remotely, which makes these services accessible to anyone, anywhere. We are working to continue developing and testing Tele-PTM.

We are currently in the early stages of conducting an RCT to evaluate the Desyncra device for tinnitus treatment. Participants are randomised to either be treated with the device or to receive “standard-of-care.” Systematic reviews have revealed that Cognitive Behavioral Therapy (CBT) has the strongest research evidence for tinnitus management, so we are using CBT as our standard-of-care control group.

A question of particular relevance to the Veterans Health Administration is whether the onset of tinnitus for a Veteran many years after leaving the military can be caused by noise or other ototoxins experienced during military service. This question is important because tinnitus is the most prevalent of all service-connected disabilities for U.S. Veterans. At any point in their lifetimes, Veterans can claim tinnitus caused by exposures during the military, and thousands of these claims are received every month. The NOISE Study (Noise Outcomes in Servicemembers Epidemiology Study), which has been underway for 3 years, enrolls military members and recently-discharged Veterans who complete comprehensive testing and questionnaires. The study is designed as a longitudinal study to evaluate Veteran participants annually for 20-30 years.

As I mentioned, we continue to develop our computer-automated tinnitus evaluation system (TES). The TES performs standard tinnitus psychoacoustic testing (loudness match, pitch match, minimum masking level, residual inhibition) plus special tests that have been developed. Our goal is to develop standardised methodology that is practical and informative for clinical and research application.

We are also collaborating with Dr Jeremy Turner who has developed a gap detection test for objective detection of tinnitus. The method measures whether a silent gap embedded in a background of sound can be detected. Numerous studies have shown that animals (following noise exposure or salicylate) with tinnitus show deficits in detecting these silent gaps. It is hypothesised that humans with tinnitus will also show such deficits. Our site is testing the method with humans.

Are there any particular challenges in working with the Veterans population with tinnitus?

I’m in research so I don’t directly see patients at the Veterans Affairs (VA) hospital where I work. As I mentioned earlier tinnitus is the most prevalent of all service-connected disabilities for Veterans. As of 2015, almost 1.5 million Veterans had received a service-connected tinnitus disability award, meaning the VA decided they have tinnitus (the disability) and that it was caused by exposures while in the military (the service connection). I am in constant touch with numerous VA audiologists who tell me about their experiences with Veterans who report tinnitus. It is clear that at least one out of three Veterans who attend Audiology clinics have tinnitus – either as a primary or a secondary problem. There are over 1300 VA audiologists working at almost 500 Audiology sites of care, and they had almost 2.4 million encounters with Veteran patients last year. Without question tinnitus is a huge problem for Veterans and for the VA. Probably the biggest challenge in meeting the tinnitus needs of these Veterans is the lack of standardisation between audiologists and between Audiology sites of care. A primary reason tinnitus services are inconsistent is that most Audiology doctoral (Au.D.) programs in the U.S. do not provide substantive training in tinnitus management. Further, despite VA recommendations for tinnitus management and the Clinical Practice Guideline for tinnitus published in 2014 by the American Academy of Otolaryngology/Head & Neck Surgery Foundation (AAO-HNSF), VA audiologists are typically unfamiliar with these recommended procedures and do not adhere to any particular protocol for tinnitus management. This is not just a VA problem, but an international problem – evidence-based guidelines for tinnitus management exist, but patients cannot expect to received evidence-based care for their tinnitus.

What aspect of your work personally gives you the greatest satisfaction?

Without a doubt, helping people is the most satisfying aspect of my work. We do not run a clinic, but our controlled trials require many participants who are significantly bothered by their tinnitus. We regularly hear back from them about how much they have been helped. I further derive great pleasure from completing studies and getting them published, which expands work in my lab around the world with the potential of helping many more people.

You recently were awarded the Jerger Career Award by the American Academy of Audiology. How did that feel?

It's an unbelievable honour for me and I had no idea I was even nominated. I discovered early on that the best research, at least in my case, comes from collaborative efforts. When you put a bunch of brains together working on the same project, it is synergistically effective. I have to give credit to the many individuals who have contributed to my research. I have been extremely fortunate to work with many very talented and gifted individuals. I am constantly amazed at the quality of work they do, and how much they know—they make me look good. The NCRAR is an ideal auditory research environment because it provides all of the necessary infrastructure. Finally, I have been supported by the VA Office of Research and Development for my entire career. They have constantly stepped up to support tinnitus research and the NCRAR. So, while my name goes on the award, it reflects the efforts of many people over many years.

You have been involved in tinnitus research for many years now. What research topic or question currently excites you?

I'm particularly interested in the use of sound to suppress tinnitus. We have known for decades that residual inhibition can be induced consistently for the majority of people with tinnitus. Residual inhibition is usually a temporary effect of tinnitus suppression lasting up to a few minutes. I am interested in the prospect of a systematic study to determine acoustical parameters that might prolong residual inhibition such that this could become a clinically viable technique. There has also been research looking at different acoustical protocols for suppressing tinnitus on a long-term basis. Sound can be "notched" around the tinnitus frequency, "matched" to the tinnitus frequency, or delivered in some way intended to manipulate brain plasticity such that tinnitus-related neural activity is disrupted, ultimately resulting in a reduction or elimination of the tinnitus percept. I have begun work in this area and find it to be an exciting line of research.

Moving away from your own research, what's your favourite piece of tinnitus research that's been done by others, and why?

That's a tough question to answer because there is so much good research out there. I have to give credit to the many "unsung heroes" who are doing tinnitus mechanisms research in their laboratories. I visited Dr Richard Salvi's lab at the University of Buffalo (in New York) not too long ago and had the opportunity of speaking with all of the researchers working in his lab. I was astounded at the variety and quality of the research that is being done there. This kind of work gives me great hope that there will indeed be a cure for tinnitus in the future.

What do you think is the biggest challenge facing tinnitus research at the moment?

The biggest challenge is finding a cure for tinnitus, i.e., some treatment that can safely eliminate the perception of tinnitus. Of course this challenge is particularly difficult because finding a cure will likely require understanding the neural mechanism(s) of how tinnitus is triggered and what sustains it over time.

What are the challenges of translating current research into clinical practice?

We can experiment with invasive techniques on animals to evaluate potential methods of treatment for tinnitus. We must use clever procedures, however, to infer the existence of tinnitus in animals and whether any manipulations actually suppress the tinnitus. With humans, we cannot normally conduct invasive techniques, but humans can tell us exactly what they are perceiving and if there is any change in their perception. So, I'd say the big challenge is in translating tinnitus mechanisms research that is done in animals to see if inferences based on the research hold true with humans. An example of this is Dr Turner's study that I've already mentioned. The next phase of his research is to determine if his gap detection method that has been shown to work in animals also works in humans.

What might you say to a sufferer who asks you whether there will ever be a cure for tinnitus?

I would first point out that there is abundant research being carried out around the world that is targeted at finding a cure for tinnitus. Tinnitus is gaining greater visibility and the number of tinnitus-related studies is continually increasing. In 2016 alone, there were 368 peer-reviewed publications listed in PubMed with tinnitus in the title. Compare this number to the approximately 10 articles per year 40 years ago, 50 per year 20-30 years ago, and 100 per year just 10 years ago. This should be encouraging news to anyone suffering from tinnitus.

Is there any advice you would give to others considering a research path in tinnitus?

I strongly endorse the clinical model of practicing evidence-based medicine. Such evidence is derived mainly from systematic reviews, which summarise results of controlled trials to specify, with minimal bias, what methods have an evidence-base in the literature. In my area of study, i.e. clinical research to develop and validate methods of tinnitus management, controlled trials are desperately needed. We can get excited about new methods, devices, etc., but until they are reported in systematic reviews as showing benefit, the credible evidence is limited or nonexistent. For these reasons, my advice for clinical researchers would be to design and perform controlled trials to test the efficacy of any method that is purported to be efficacious.

Finally, is there anything else you would like to share with our readers?

This question could really put me on a soapbox because I am passionate about the need to standardise the field of tinnitus management. In spite of what seems to be a vast amount of research taking place, there is little evidence that researchers are collaborating to make their research more efficient. This “silo” approach could be greatly improved by creating an international committee of the most prominent tinnitus researchers and assigning them the task of working together to establish common goals and methodologies for attaining those goals. Standardisation in tinnitus management techniques is needed and that will require some kind of credentialing program for clinicians to become qualified and certified “tinnitus care providers.” Such a program will require a panel of experts to create a program of official verification that a provider has achieved criterion standards regarding training, supervision, and experience. Until we reach this point, the tinnitus sufferer is mostly at the mercy of anyone who claims to offer help.

“The biggest challenge is finding a cure for tinnitus, i.e., some treatment that can safely eliminate the perception of tinnitus. Of course this challenge is particularly difficult because finding a cure will likely require understanding the neural mechanism(s) of how tinnitus is triggered and what sustains it over time."

- Dr James Henry

PROFESSOR DAVID BAGULEY
Professor in Sciences / Deputy Director
University of Nottingham / NIHR Nottingham Biomedical Research Centre

David Baguley is a Professor of Hearing Sciences at the University of Nottingham, working in the Division of Clinical Neurosciences (Faculty of Medicine), and the Otology and Hearing Group. He heads up the Clinical Hearing Sciences group within the NIHR Biomedical Research Centre. David's particular research interests lie in the area of iatrogenic tinnitus and hearing loss associated with the use of platinum-based chemotherapy in adult survivors of cancer.

For over 30 years David was the Head of Audiology at Cambridge University Hospitals NHS Foundation Trust, an in the last 5 years the Head of Auditory Implants and of Newborn Hearing Screening also.

David has co-authored over 150 research papers, many book chapters, and has co-authored and edited several books.He has twice been awarded the Shapiro Research Prize of the British Tinnitus Association, and in 2006 received an International Award in Hearing from the American Academy of Audiology.

THE PHARMACOLOGY OF TINNITUS : OTOTOXICITY AND TREATMENT

Professor David Baguley

The potential for there to be a drug treatment for troublesome tinnitus has been a topic of substantial and long standing interest, and questions about this arise very often in the clinic. Many compounds of interest have been trialled, and of 219 recruiting or completed tinnitus studies described on clinicaltrials.gov, 68 (31%) involve drug treatments or dietary supplements. One of the reasons for the sparse progress to date has been the lack of effort: this has not been an area where financial nor time resources have been deployed until relatively recently. In this section we review what was reported regarding tinnitus and pharmacology in 2016, including tinnitus caused by drug treatments, how that might be prevented, and tinnitus treatment by drugs. The literature search that underpinned this section was conducted on PubMed, used the ley words tinnitus and drug, considered human studies only, and papers published in English between 1.1.16 and 31.12.16.

Ototoxicity and its prevention

Platinum-based chemotherapy is highly effective in treating cancer, and has contributed to modern survival rates which approximate 66% five years after diagnosis [1]. These treatments are ototoxic however, leading to permanent hearing loss and tinnitus in many cancer survivors, which can potentially lead to reduced quality of life in survivorhood. The extent of ototoxicity appears to depend on several factors, including genetic susceptibility and cumulative dose among others [1]. Van As *et al* published a Cochrane Review in 2016 [2] of different infusion durations of cisplatin in children, and how this might potentially prevent ototoxicity: only one randomised controlled trial was identified. This had only immediate post treatment follow-up, and no consideration of tinnitus. In a context where post-treatment development or progression of hearing loss can occur with cisplatin treatment

Figure 1
Young girl receiving chemotherapy. Image copyright National Cancer Institute.

in adults, and where tinnitus can develop in 40% of patients, this is inadequate, as van As and colleagues discuss.

Some cancer patients receive both platinum-based chemotherapy and radiotherapy, and ototoxicity is a major concern when the tumour is in the head and neck, such that the cochlea is doubly vulnerable. Niemensivu *et al* [3] noted that patients undergoing high dose cisplatin and radiotherapy treatment "will suffer from hearing deficits" but sought to investigate the ototoxicity effects of low dose cisplatin, and radiotherapy. Whilst the report of reduced hearing loss and tinnitus compared with higher doses of cisplatin are encouraging, this study did not involve high frequency audiometry (10-16kHz), and the patient numbers (n=9) were too low for any definitive conclusions.

Other drugs that can cause ototoxic tinnitus include quinine and salicylate, and their modes of action were studied by Alvan *et al* [4] . Whilst there is a consensus that both drugs affect the cochlear Outer Hair Cells (OHC), which are involved in the fine-tuning of the mammal cochlea, rather than the Inner Hair Cells (IHC), which convert the vibrational energy of sound into neural impulses, Alvan and colleagues propose that the OHC impact of quinine and salicylate is accomplished by quite different molecular mechanisms, and this may have important implications for prevention, and deeper understandings of cochlear dysfunction.

Treatment: reviews

Literature reviews can be of major value, allowing assessment of the quality of published evidence, and the synthesis of data across studies to increase the strength of a particular finding. Several reviews in the area of drug treatments for tinnitus were published in 2016 from quite different perspectives. Nguyen *et al* undertook a fascinating and innovative review [5] of patents taken out between 2011 and 2015 regarding drug delivery for inner ear disorders. The 34 patents they identified ranged from new therapeutic agents, to systems of sustained release, to new technologies for drug delivery. Whilst tinnitus was not the only topic of this paper, clearly this is an area of great interest regarding treating tinnitus, and this paper makes a significant contribution to the literature.

One particular option for drug treatment of inner ear disorders is the intra-tympanic administration of steroids, and Lavigne *et al* reviewed the evidence [6]. Their conclusion was that they identified some but not unequivocal evidence that intra-tympanic steroid injection may be beneficial for some inner ear disorders that include tinnitus in their symptom profile, such as Ménière's disease and idiopathic sudden sensorineural hearing loss, and that there might be some improvement in the associated tinnitus for some patients. There was no evidence of benefit for tinnitus alone however.

An exploratory review of an interesting idea was

Figure 2
Ginkgo biloba

undertaken by Smith and Zheng [7]. They proposed that tinnitus may be considered as a form of 'sensory epilepsy', based in part on the finding that some anti-epileptic drugs may improve tinnitus in some cases. They then explore the possibility that cannabis and related compounds may have an anti-epileptic effect, and thus may improve tinnitus. Whilst this is essentially speculative, the fact that some in the tinnitus community are prepared to envisage innovative hypotheses and proposals is encouraging.

Treatment: clinical trials

Two papers each reporting the results of a clinical trial were published in 2016. Singh *et al* investigated the potential benefits of vitamin B12 in a pilot study[8]. This was a placebo controlled double blind trial and whilst the results of the pilot indicated some benefits for tinnitus severity, there are some caveats. The outcome measures used were not validated and robust instruments, and the treatment and placebo groups both contained a mixture of vitamin B12 deficient and sufficient individuals, who might be expected to have quite different reactions to the six weekly intramuscular B12 injections that comprised the treatment under investigation.

Polanski *et al* investigated the potential benefits of antioxidant therapy [9] for tinnitus in older patients, the treatments under study comprising Gingko biloba, vitamins C and E, and papaverine hydrochloride versus an inert placebo. No benefits for tinnitus with these therapies was found using the Tinnitus Handicap Inventory [10] as an outcome measure.

Whilst not a trial, some other data regarding dietary supplements for tinnitus was published in 2016. Coelho and colleagues [11] undertook a large survey (n=1788) across 53 countries, and 23.1% of the respondents self-reported taking dietary supplements for tinnitus. There were reported benefits for sleep, emotional state, concentration, and for hearing, with some adverse effects including headaches. The authors reflected on the potential biases in a survey of this kind, and concluded that whilst supplements are not generally beneficial for tinnitus, in some patients there might be an effect.

Discussion

Although there were some publications of interest regarding potential drug treatments for tinnitus in 2016, they were not replete, and this is an area that might benefit from sustained and comprehensive efforts.

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DR DEREK HOARE
Associate Professor
NIHR Nottingham
Biomedical Research Centre

Derek trained in nursing at the University of Brighton and then completed a PhD in neuroscience at University of Manchester. He is now Associate Professor in Hearing Sciences at the NIHR Nottingham Biomedical Research Centre, University of Nottingham.

There he leads a programme of research on tinnitus and hyperacusis with particular interests in developing assessment tools and low-intensity psychological and self-help interventions. Derek is a steering group member of TINNET working group 1 (Clinical), a network of clinicians and researchers working to develop pan-European clinical practice guidelines for tinnitus. He is also chair of the British Society of Audiology Tinnitus and Hyperacusis Special Interest Group.

INTERNET-BASED TREATMENTS FOR TINNITUS

Dr Derek J Hoare

The internet is unquestionably a phenomenal platform for health information, research, rehabilitation programmes, and self-management programmes. There is evidence too that internet-based treatments can lead to improvements in psychological distress, health behaviour, and disease control [1]. Interestingly, Henshaw *et al* found that in adults aged 50-74, hearing loss was associated with greater computer skills and internet use than having no hearing loss [2]. So, internet-based treatments might be particularly suited to those with hearing problems, as is the case for most people who have tinnitus.

In the field of audiology interest and investment in internet-based assessments and treatment programmes is on the increase, so much so that the international 'Internet and Audiology' conference will be in its third annual meeting later this year. There is a clear sense in the field that the internet represents new opportunity to better use clinical expertise for the benefit of people with hearing difficulties and related conditions such as tinnitus [3].

Internet-based treatment for tinnitus might include, for example, asynchronous clinician contact, interactive homework, or the provision for use of audio, video, or text files [4]. Eight research papers on this topic were published during 2016. Two papers describe work so far on different tinnitus self-management programmes. Three papers considered effectiveness of internet-based treatments: one randomised controlled trial (RCT), one observational study, and one systematic review. A further three papers consider how internet-based treatments for tinnitus might work.

Newly-developed internet-based treatments

Internet-based treatments for tinnitus that are on the horizon are described in Greenwell *et al* [5] and Beukes *et al* [6] both of whom are UK-based authors.

Greenwell *et al* describe their protocol for a mixed-methods process evaluation of how people use and interact with the Tinnitus E-Programme [7]. This 10-week internet-based self-management programme provides

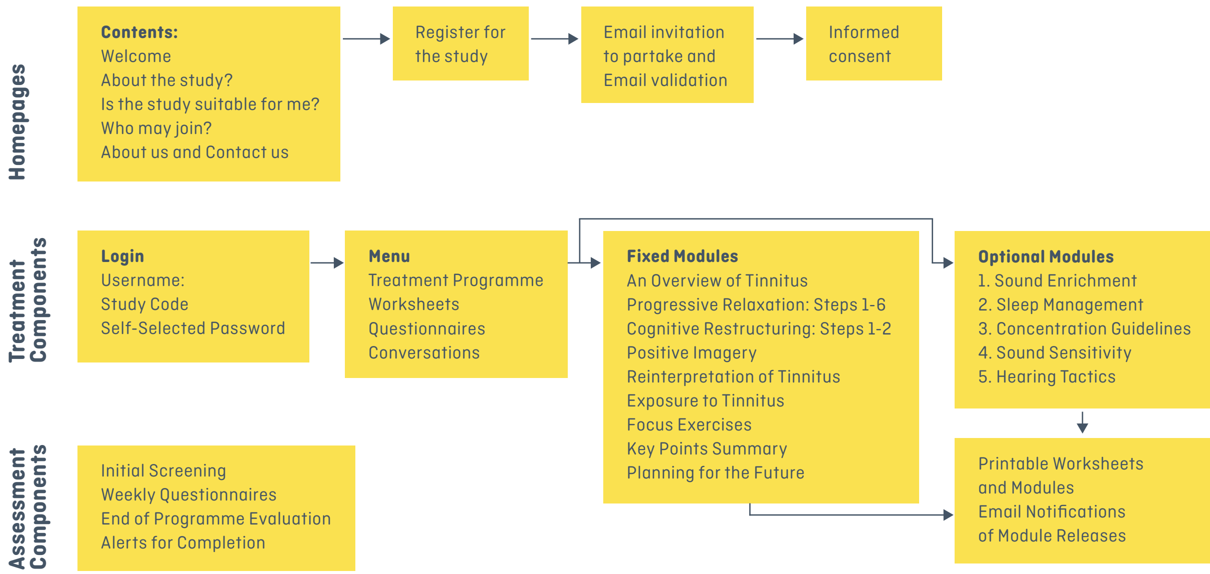

Figure 1
Outline of the components used for iCBT for tinnitus [6]

downloadable educational materials, relaxation exercises and training, brief cognitive restructuring skills training, optional social support in the form of a moderated online discussion forum, and information about books and other websites that might be useful.

The programme is self-completed over 6 weeks followed by a 4-week 'maintenance' period where individuals continue to practice the skills they have learned. People can self-monitor their progress by completing a tinnitus questionnaire [8].

The purpose of a process evaluation is to develop a deep understanding of how people experience a treatment, an essential first step when evaluating treatments that are complex. To do this Greenwell *et al* outline two parallel mixed-methods studies. Study 1 is an online survey to gather views from people who already have experience of the programme. Study 2 involved new users who completed the 10-week programme before taking part in an in-depth interview, and reported their use of the skills learned and how well they were able to implement the skills in their everyday lives. The findings from both studies will be used to optimise the Tinnitus E-Programme before effectiveness is tested in a clinical trial. At the time of publication Study 1 was still open to recruitment and Study 2 was completed.

In the second paper, Beukes *et al* describe the development process of their treatment, a clinician-guided internet-based cognitive behavioural therapy (iCBT), and the technical functionality testing they went through to identify any areas for improvement. The express aim of the treatment is to "maximise behavioural change by offering various techniques within a comprehensive intervention that focuses on addressing the physical, emotional and daily effects of experiencing tinnitus" (p.7). The treatment comprises compulsory modules on progressive relaxation, cognitive restructuring, use of positive imagery, reinterpretation of tinnitus, exposure therapy, focus exercises, and planning for the future. There are also optional modules on sound enrichment, hearing tactics, and sleep, concentration, and sound sensitivity problems.

In their study the iCBT was first evaluated in the development stage by a group consisting of specialist audiologists, a hearing rehabilitationist, and two members of a tinnitus support group. iCBT was then tested in a group of 29 adults with significant tinnitus distress. All participants completed a satisfaction questionnaire developed specifically for the study rating various aspects of the programme including usability, suitability of content, presentation, suitability of iCBT for people who have tinnitus, and the appropriateness and clarity of the exercises involved.

Overall, satisfaction was high and the main refinements indicated related to technical functionality. This treatment is subject to an ongoing randomised controlled trial (clinicaltrials.gov: NCT02370810). Importantly, the studies described by both Greenwell *et al* and Beukes *et al* were guided by the Medical Research Council guideline on developing and evaluating a complex intervention [9]. This guideline urges careful and iterative development and feasibility testing of new complex treatments before they can be considered ready to evaluate in a clinical trial. In addition, publication of the process of development and feasibility testing such as was done by Greenwell *et al* and Beukes *et al* is important for transparency and to promote best practice in the field of internet-based treatment development.

Do internet-based treatments work?

Measures of effectiveness of internet-based treatments for tinnitus were reported in two clinical studies and one systematic review published in 2016. In the first clinical study, Kim *et al* describe a treatment using individualised 'notched' music delivered from a smartphone app, combined with the herb Ginkgo biloba [10]. Twenty-six patients reporting persistent bothersome tinnitus were recruited to the study and were instructed to (1) listen to the notched music for 30–60 minutes per day, and (2) take Ginkgo biloba (Ginexin-F 80-mg tablets) twice a day, for 3 months. The effects of the combined treatment were measured using the Tinnitus Handicap Inventory (THI) questionnaire [11]. Various demographic data were also collected using clinical questionnaires that measure depression, anxiety, and sleep quality, to examine whether these factors affected treatment success. After treatment, there was a modest reduction in tinnitus questionnaire scores overall (34 points before treatment and 23 after) which does not equate to a clinically meaningful change.

There are a number of issues to highlight with the study by Kim *et al*. Not least is that the study involved two different treatments combined and no 'control' group. As such it cannot be determined if any improvements in individuals might be associated with one or other part of the treatment, or indeed if any improvement was simply due to spontaneous improvements in tinnitus that happened over the three month course of the study. It is also unclear why these authors used Gingko biloba in their study. They provide no rationale for it and in discussing limitations of the study refer to one of their own studies as evidence of it having no beneficial effect on tinnitus. Rather, its use clinically is recommended against as it is associated with no tinnitus benefit and some negative side effects and common drug interactions [12].

The only RCT of an internet-based tinnitus treatment to be published in 2016 came from Weise *et al* who compared the effectiveness of iCBT to participation in a moderated online discussion forum [13]. iCBT was delivered as described earlier for Beukes *et al* with the exception that the clinicians guiding the treatment were CBT therapists or clinical psychologists. They used the discussion forum to control for non-specific effects of treatments such as treatment expectancy effects. Participants were randomly allocated to the two different conditions with 62 people in each study group, and assessed for tinnitus severity and associated symptoms before and after treatment. For the iCBT group they also measured symptoms at six and 12-month follow-up. On their main measure of effect, the THI, they found a significant and clinically meaningful improvement in scores for the iCBT group (53 points before treatment and 33 after) compared to the discussion forum group which had a small reduction in tinnitus score (52 points before treatment and 46 points after). Improvements in the iCBT group were maintained at six and 12 months after treatment (35 points before treatment and 29 after). Based on this and previous evidence of effectiveness they conclude that the implementation of iCBT for tinnitus into routine health care is an important next step to improving access to treatment for patients with tinnitus.

The combined evidence for the benefits of self-help interventions for tinnitus was systematically reviewed by Greenwell *et al* [14]. In this paper, the authors reviewed controlled clinical trials and reported on measures of tinnitus distress, functional management, anxiety, depression, and quality of life. They also used a behaviour change techniques taxonomy and the PRISMS taxonomy of self-management components to systematically describe the interventions. Just five studies were included in the review, and only two evaluated internet-based treatments (iCBT) for tinnitus. Those studies showed that

- iCBT led to a reduction in tinnitus distress but not depression, and
- iCBT that is guided by a therapist may be more effective than unguided iCBT.

Taken together with the more recent study from Weise *et al* it can be concluded that iCBT is an important avenue of further development.

How internet-based treatments might work?

To optimise the benefit that might be had from internet-based treatment it is important to consider at all stages how they might work. Effectiveness may be as much about the way the treatment is delivered as it is about treatment content for example. So how do internet-based treatment components, and a user's interactions with them, lead to the desired beneficial effects? Greenwell and Hoare explored the presence of four key interactive design features (social context and support, contacts with the intervention, tailoring, and self-management) across internet-based audiology rehabilitation and self-management interventions including those for tinnitus [15]. The review also asked whether there is evidence of these design features being important to the effects of the intervention. Five treatments were identified as representative examples of work in the field, two of which were treatments for tinnitus (iCBT and the Tinnitus E-Programme, as described earlier). Interestingly, both treatments were found to use social context and support and contacts with the intervention (e.g. therapist contact, email/phone contact) and self-management (e.g. homework assignments, self-completing and scoring clinical questionnaires) and neither treatment use any form of tailoring. Tailoring involves the provision of individualised information based on certain characteristics, e.g. only providing information on sleep management to those people who report their tinnitus impacts on their ability to sleep well. This review concluded that future studies should explore the role of tailoring as a potential mediator of more benefit from internet-based treatments, and the amount and combinations of design features that lead to maximum benefit. As the two tinnitus treatments in this review used the same design features they cannot be contrasted on that basis.

A mixed methods approach was used by Heinrich *et al* who explored what makes people who have tinnitus seek help, and what motivates them while they undertake iCBT [16]. These are important questions as studies of internet-based treatments often report high attrition after initial engagement, and some patients prefer face-to-face therapy to iCBT. Heinrich *et al* explored these issues with an open ended questionnaire sent to 112 tinnitus patients before and after completing iCBT for tinnitus. Patients reported six factors that would motivate them to continue with treatment, namely potential for success, training/learning something new, personal disposition, prospect of success, evidence of it being effective for others, and support from the study team or their social environment. Naming specific tinnitus-related problems as a reason for engaging with iCBT was associated with greater improvement after, as was describing an active involvement in the treatment. These authors conclude the need for further hypothesis driven testing to confirm their exploratory results.

Figure 2
Laptop user accessing an internet-based treatment (picture posed by model)

Predicting benefit

The final paper reported here came from Lindner *et al* who asked whether cognitive flexibility (how well we can switch between thinking about two different concepts) predicts the benefit that people report after completing internet-based psychological treatments for tinnitus or other disorders [17]. Fifty-three people took part in the tinnitus trial and completed the Wisconsin Card Sorting Test (used to measure cognitive flexibility) [18] before treatment with iCBT. The authors hypothesised that if a person has greater cognitive flexibility then they are more able to learn and use the cognitive restructuring techniques that are part of iCBT, and so would report more improvement in their tinnitus. However, they found no significant relationship between treatment gains and scores on the Wisconsin Card Sorting Test, concluding that lower cognitive flexibility, as measured by this test at least, should not reflect the likelihood of benefit from iCBT.

Conclusion

Educational and psychological treatments are not always readily accessible yet are acknowledged as beneficial to people with tinnitus. As such, internet-based treatments with their global reach provide an alternative to those unable or indeed unwilling to access traditional clinical services. They may also represent useful additions to clinical services either complementing what treatment is currently given, or providing resources that can be accessed as needed between clinic appointments. Internet-based treatment is viable and likely desirable to clinicians and people with tinnitus. However, care is needed if treatments are to be delivered in the most effective way. Whilst the content of an intervention might be excellent, if the intervention lacks key design features then its potential effectiveness may never be realised. There is every indication to continue and drive forward this line of research and treatment.

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DON MCFERRAN
Consultant ENT Surgeon
Colchester Hospital University
NHS Foundation Trust

Don has worked as an ENT surgeon since the mid 1980's and has been a Consultant in Colchester, Essex since 1999. He trained at Queens' College Cambridge and Cambridge University Medical School. He has published widely on a diverse range of ENT topics including paediatric tinnitus and has co-authored two tinnitus books – one for professionals and one self help book for people with tinnitus and hyperacusis. Don is a Trustee of the British Tinnitus Association.

TECHNOLOGICAL MANAGEMENT OF TINNITUS: AN UPDATE

Don McFerran

The ultimate hope for most tinnitus sufferers and clinicians is that a 'pill for tinnitus' will be developed and, indeed, there is considerable pharmacological research being conducted. Other therapeutic options being explored include talking therapies and treatments that incorporate physical modalities such as electrical, magnetic, sound, vibration or laser light stimulation. A literature search for treatments using physical modalities was undertaken, running from the end of 2015 to the current time. The findings are presented in this brief review.

Novel sound therapies

Sound therapy in multiple guises has been one of the main staples of tinnitus management over the years. Sounds that have been used vary from simple broadband sound to complex spectrally manipulated sounds. Despite its widespread usage, a robust evidence base for the use of sound therapy is still lacking.

Spectrally altered music

Several studies have been undertaken on the use of notched sound: patients listen to sound – usually music – that has been modified such that the sound is reduced or completely removed in the frequency range surrounding the pitch of the patients' tinnitus. The rationale of this is that by stimulating the auditory system except in the frequency range around that of the tinnitus, maladaptive cortical reorganisation is reversed. Stein *et al* described a randomised controlled trial that recruited 100 participants [1]. 83 finished the treatment course. The chosen primary outcome measure was the Tinnitus Questionnaire (TQ) [2] and on this measure no benefit was seen in the treatment group compared to the placebo group. A small benefit was however demonstrated on a visual analogue scale of tinnitus loudness.

Kim *et al* developed a smart phone app to deliver notched music therapy and undertook a small pilot study (n=26) to assess its effect [3]. Patients were also given Ginkgo biloba. Some benefit was seen but as this was a small uncontrolled study, the results must be interpreted with caution.

Li *et al* reported using spectrally altered music in a randomised controlled trial of 50 tinnitus subjects [4]. A computer model was used to generate customised classical music therapy based on patients' individual tinnitus parameters and hearing levels. The placebo group listened to unaltered classical music. The treatment group demonstrated significantly less tinnitus distress as assessed using the Tinnitus Handicap Inventory (THI) questionnaire [5]. There was however a high level of attrition, with the results of only 34 of the 50 participants being analysed.

Acoustic neuromodulation

Abnormal neuronal synchrony within the central auditory system has been proposed as one of the pathophysiological mechanisms of tinnitus and a commercial device is available that delivers a customised auditory stimulation with the aim of disrupting this increased synchrony. This technique has become known as acoustic co-ordinated reset neuromodulation. Several studies investigated this technique. Hauptmann *et al* studied the feasibility of using existing consumer mobile devices to deliver the therapy and concluded that this is a viable option [6]. Zeitler and Tass presented the mathematical arguments underpinning a two-stage co-ordinated reset protocol [7]. Hauptmann *et al* described a study using acoustic co-ordinated reset neuromodulation on 200 patients with chronic tonal tinnitus [8]. The trial was an open-label, non-randomised, non-controlled study. 189 participants completed the trial and results showed statistical improvement over a 12-month period.

Nocturnal sound stimulation

In 2014, Pedemonte *et al* made the observation that sensory processing continues during sleep and that there is a relationship between sleep and learning [9]. They performed a small (n=10) proof of concept study measuring patients' electroencephalogram waves during sleep whilst a sound stimulus mimicking their tinnitus was applied. In a follow-up study by Drexler *et al*, the same team assessed tinnitus in 12 patients who received highly customised nocturnal sound therapy that reproduced their tinnitus, delivered via a small portable audio player and earbuds [10]. Significant improvement was seen in all outcome measures over a three-month period. The device is now commercially available. Its use is only recommended for specific tinnitus pitches. It will be interesting to see if larger independent trials can replicate the developers' findings.

Sound therapies with neural stimulation

As our understanding of tinnitus improved, it was recognised that other pathways outside the classical auditory system play a role in the generation of the symptom. Simultaneous stimulation of these neural and auditory pathways is being explored as a mode of managing tinnitus.

Sound and trigeminal nerve stimulation

One study recently published investigated the simultaneous stimulation of auditory and trigeminal nerve pathways [11]. A complex auditory stimulus was delivered via headphones at the same time as low-level electrical stimulation of the front of the tongue. The treatment was well tolerated and, in compliant patients, all outcome measures showed significant improvement. This was however an open-label pilot study undertaken by the developers of the treatment and further more rigorous independent research is required.

Sound and vagal stimulation

Stimulation of the vagus nerve has long been recognised as one means of modulating central neural activity. Following a series of animal experiments [12], the possibility of treating tinnitus patients with sound therapy paired with stimulation of the vagus nerve using either a surgically implanted electrode or by transcutaneous stimulation has been explored.

A pilot study [13] used electrical stimulation of the vagus nerve by applying an electrode to the concha of the left external ear together with sound stimulation using notched music. This trial demonstrated that the transcutaneous route of stimulation is safe, well tolerated and can improve symptom scores, but as it was relatively small (n=30) and uncontrolled the findings need to be interpreted with care. De Ridder *et al* published a case report of a patient with refractory tinnitus who showed improvement after implantation of a vagal nerve stimulator [14]. They paired vagal stimulation with sound stimulation and showed that bimodal stimulation improved the patient's symptom but sound stimulation on its own did not. Neither of these studies provide enough evidence to recommend this treatment modality and further work is needed.

Somatosensory stimulation

There are putative links between auditory and somatosensory neurones in the brainstem and stimulation of somatic sensory pathways has been suggested as a way of modulating tinnitus. A small handheld vibrating device, resembling a rechargeable electric toothbrush but with a range of solid tips instead of a brush, is currently being marketed for use in a variety of medical conditions including tinnitus. A study by Jonsson *et al* concluded that it does result in temporary reduction of tinnitus but this is due to residual inhibition from the sound created by the device rather than due to somatic sensory stimulation [15].

Magnetic brain stimulation

Repetitive transcranial magnetic stimulation (rTMS)

It is 14 years since the first peer reviewed scientific paper was published on the subject of rTMS for the treatment of tinnitus. It is therefore perhaps a bit surprising that there are still no definitive answers regarding this modality. An optimistic note was sounded by Soleimani *et al* who performed a systematic review and meta-analysis of rTMS for tinnitus [16]. Results from 15 randomised controlled trials were analysed with the conclusion that rTMS is beneficial for tinnitus – albeit at a modest level. However, the studies that were subjected to meta-analysis showed considerable heterogeneity and it is doubtful whether performing meta-analysis was justified.

rTMS continues to be an attractive topic for research with a dozen papers published between the last quarter of 2015 and the present. These addressed a wide variety of research questions including the optimum site and duration of treatment, the best outcome measures to use, whether neuronavigation helps the outcome, whether repeated courses of treatment are effective, whether tinnitus specific biological treatment effects can be detected and whether there are any predictors of which people will benefit from rTMS. A brief synopsis of these studies is presented in Table 1.

Study (lead author, year and location)	**Design including stimulation site(s)**	**n**	**Main outcome measure(s)**	**Results / conclusions**
Noh 2017 Seoul, South Korea [17]	Single site (left DLPFC) vs dual site (left DLPFC and left AC) stimulation.	17	THI, VAS	Dual stimulation more effective than single site.
Wang 2016 Shanghai, China [18]	Factor analysis following left TP stimulation.	289	VAS	Tinnitus suppression better with shorter duration tinnitus, normal hearing, absence of sleep disturbance.

Study (lead author, year and location)	Design including stimulation site(s)	n	Main outcome measure(s)	Results / conclusions
Wang 2016 Shanghai, China [19]	Left TP. Study of outcome measures.	14	GIN [20], VAS	GIN potentially a useful research tool.
Lehner 2016 Regensberg, Germany [21	Single site (left TP) vs triple site (left DLPFC and left and right TP) stimulation.	49	TQ	Both groups improved. Triple site stimulation better at 90 days. No long term statistical difference between groups.
Schecklmann 2016 Regensberg, Germany [22]	Pilot study. Neuronavigated theta burst to left AC vs sham control.	23	TQ, numerical rating	Both groups improved. No difference between groups.
Labar 2016 New York, USA [23]	Feasibility study for long term treatment. Contralateral TP stimulation for unilateral tinnitus. Left TP stimulation for bilateral tinnitus. Initial responders treated for 5 months.	8	THI, mini TQ	4 responders at week 5; 3 at week 10; 1 at week 30. Good compliance. Long term treatment feasible.
Roland 2016 St Louis, Missouri, USA [24]	Left TP vs sham.	30	THI, functional connectivity MRI scan	No changes in neural connectivity.
Wang 2015 Shanghai, China [25]	Pilot study. Neuronavigated by EEG, Left TP or sham.	7	THI, VAS	EEG navigation improved outcome.

Study (lead author, year and location)	Design including stimulation site(s)	n	Main outcome measure(s)	Results / conclusions
Kreuzer 2015 Regensberg, Germany [26]	Pilot study. Left TP and ACC vs Left DLPFC and TP.	40	TQ	No difference between groups.
Folmer 2015 Portland, Oregon, USA [27]	Temporal stimulation with active coil or a placebo coil that had a metal plate blocking most of the magnetic field.	64	TFI [28]	Statistically more responders in active group: 56% vs 22%.
Lehner 2015 Regensberg, Germany [29	Participants who had previous rTMS could self-refer for a second course. Gap between courses 20.55 weeks, +/- 18,56. Multiple stimulation protocols.	23	TQ	Improvement seen particularly among those whose reason for seeking second treatment was that their tinnitus had worsened.
Schecklmann 2015 Regensberg, Germany [30]	EEG changes following rTMS. Multiple stimulation protocols.	20 tinnitus 20 non-tinnitus controls	EEG	Left TP and right frontal stimulation altered the EEG in tinnitus patients only.

Table 1
Summary of recent experimental studies using rTMS to treat tinnitus.

Key to abbreviations:

AC	Auditory Cortex,
ACC	Anterior Cingulate Cortex,
DLPFC	Dorsolateral Prefrontal Cortex,
EEG	Electroencephalogram,
GIN	Gap in Noise,
MRI	Magnetic Resonance Imaging,
THI	Tinnitus Handicap Inventory,
TP	Temporoparietal,
TQ	Tinnitus Questionnaire,
VAS	Visual Analogue Scale.

Figure 1
A patient undergoing rTMS
(image courtesy of Magventure)

Although these studies offer some worthwhile new information regarding rTMS for tinnitus, the more interesting recent papers on the subject are not clinical studies but editorial explorations of how to improve our investigation of rTMS. Three publications [31] [32] [33] make similar points: evidence regarding rTMS for treatment resistant depression was unclear until large multicentre trials were devised. These proved that rTMS does have a role in depression, for specific patients and with specific treatment protocols. All these editorials recommend that a similar approach is taken for tinnitus.

One problem with rTMS is that the stimulating device is very noisy, creating loud clicks with intensities estimated to exceed 140dB. This means that it is possible some of the effect of this modality is through sound stimulation rather than electromagnetic stimulation. Furthermore, there is a risk that the loud sounds could damage the auditory system and potentially could exacerbate tinnitus. The noise also means that some studies that have been described as double blinded may have had ineffective blinding. An interesting paper discusses potential ways of producing quieter rTMS equipment [34].

Magnetic brain stimulation in conjunction with other treatment modalities

In addition to trials as a stand-alone therapy, rTMS has been investigated as a component of combination therapy.

rTMS and relaxation

In a small proof of concept trial 42 patients were treated with TMS while listening to relaxation audio recordings [35]. 38 subjects finished the treatment course and although trend towards improvement was seen this did not reach statistical significance.

rTMS and laser

In another small trial, 32 patients were randomly allocated to three groups, receiving TMS alone, low level laser therapy alone or a combination of the two treatment modalities [36]. All but two patients completed the study. Combined therapy demonstrated improvement whereas using single modality treatment did not. However, numbers in each arm of the trial were low and the maximum follow-up time at four weeks was short. This trial is best regarded as a pilot.

Transcranial electrical brain stimulation

Transcranial direct current stimulation (tDCS)

Shortly after humans learnt how to harness electrical energy we have been studying it as a means of modifying a wide range of ailments. Tinnitus is no exception. Hoare *et al* produced a detailed review of this treatment modality with regard to tinnitus [37]. Previous studies have suggested that low-level transcranial direct current stimulation (tDCS) of certain areas of the brain can transiently reduce several tinnitus parameters. In a small (n=22) but randomised, placebo-controlled, double-blind trial [38] Forogh *et al* investigated direct current stimulation of the left temporoparietal area in tinnitus patients, finding no statistical difference between active stimulation and sham stimulation. The results of this study concur with a similar trial [39] that investigated application of tDCS to the auditory and prefrontal cortices of 42 patients with tinnitus, finding no tinnitus effect. The results of these two trials are at variance with some of the previous work and clearly further investigation is needed.

Highly Defined transcranial direct current stimulation (HD-tDCS)

Standard tDCS uses large sponge electrodes which deliver the electrical stimulus to a large area of scalp with the electrical current spreading to deep brain structures. A variation of this technique uses smaller gel electrodes which allows more precise delivery, limiting the stimulating effect to superficial areas of the brain. This method is called Highly Defined Transcranial Direct Current Stimulation (HD-tDCS) and its effects on tinnitus have been recently studied [40]. This was a small preliminary study to try and determine optimum stimulation parameters and concluded that stimulation at 2mA for 20 minutes was the most effective. Stimulation was applied to the left temporoparietal or dorsolateral prefrontal cortex with equal efficacy. Further work on this modality is awaited.

Transcranial random noise stimulation (tRNS)

A modified form of transcranial electrical brain stimulation has recently started clinical trials. In this form of stimulation, the electrical current is varied randomly within a predetermined bandwidth. Known as transcranial random noise stimulation (tRNS) it has been investigated for use in tinnitus.

Kreuzer *et al* issued a case report of a patient who described tinnitus in association with erythema and pain of the ipsilateral external ear [41]. This 'Red Ear Syndrome' had proved treatment resistant and tRNS was suggested as a possible way of reducing the tinnitus component. To the clinicians' surprise the pain improved but not the tinnitus.

To *et al* studied 40 tinnitus patients who received either bifrontal tDCS on its own or bifrontal tDCS followed by bilateral auditory cortex tRNS and concluded that multisite treatment was more effective [42].

Direct electrical brain stimulation

Few patients with tinnitus would consider subjecting themselves to invasive brain surgery but for a small minority this remains a therapeutic option. De Ridder *et al* reported two patients who had electrodes surgically implanted on the dorsal anterior cingulate cortex [43]. One patient responded to this treatment: the other did not.

Electrical ear stimulation

Although much of the interest in electrical and magnetic stimulation for tinnitus is directed at stimulation of brain pathways, some researchers continue to study direct stimulation of the ear. Mielczarek *et al* report a small (n=12) uncontrolled pilot study, stimulating the ears of six patients with unilateral tinnitus and six with bilateral tinnitus [44]. Some improvement of visual analogue scale measures of tinnitus was observed and electroencephalographic changes were detected in a subgroup of the participants.

Laser to the ear

There were no new publications regarding laser treatment of tinnitus as a stand-alone therapy during the time period of this review.

Conclusion

The majority of studies in this review are small with many being described as pilot studies or feasibility studies. Methodology is often poor with inadequate controls. In most cases the treatment modality being tested has been available for decades – in some cases centuries. It is therefore disappointing to see the overall quality of the research. If this field of tinnitus is to advance, better methodology and large multisite trials are urgently required. This is particularly so for rTMS where there is a suggestion that this may be clinically helpful for a subgroup of tinnitus patients.

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Conflicts of interest: I have undertaken work for (and been paid by) the following drug companies who were/are trialling drugs for tinnitus or conditions that incorporate tinnitus as one of the constituent symptoms: GSK, Autifony, Otonomy. I have received fees for lecturing about the treatment - including drug treatment of tinnitus.

REMEMBER TO ENJOY THE JOURNEY:
Dr Susanne Nemholt Rosing talks to Nic Wray

DR SUSANNE NEMHOLT ROSING
Master of Arts in Speech Pathology
University of Copenhagen

Susanne Nemholt Rosing has a Master of Arts in Speech Pathology and Audiology from the University of Copenhagen in 2003. She had almost 10 years of clinical practice working in the field of rehabilitative audiology and especially in tinnitus and hyperacusis management before she started her own research. Susanne completed her PhD thesis "Tinnitus and Hyperacusis Among Children and Adolescents in Denmark" in November 2016 at the University of Southern Denmark. In June 2017, Susanne started a post-doctoral project on interventions for childhood tinnitus and hyperacusis and the development of specialist paediatric tinnitus and hyperacusis services in Denmark.

NIC WRAY
Communications Manager
British Tinnitus Association

What made you first interested in tinnitus?
After I finished my Master of Arts in Speech Pathology and Audiology at the University of Copenhagen in 2003, I started working in the field of rehabilitative audiology and especially in tinnitus and hyperacusis management. For me, the interaction and the importance of paying close attention to each person's story and beliefs fascinated me, and to be part of the process where each individual found a way back to their life with tinnitus was very inspiring.

How did your research career develop to where it is now?
Since 2010, I have lectured in audiological education in Denmark at all levels from care givers to university degree students, where I also have been a supervisor for audiological students. My research career started because I was left wondering. Sometimes children and young people were referred to me because of their tinnitus or hyperacusis and I wasn't sure how to address these children. This was the foundation for my PhD project "Tinnitus and Hyperacusis Among Danish Children and Adolescents", where I was so lucky that David Baguley agreed to be part of my supervisor team and helped me in many ways both academically and personally. Although I had almost 10 years of clinical practice before I entered the academic world, I still consider myself as a novice.

What research are you currently involved in?
In June, I'm starting my postdoc project, which (if we can get funding) will focus on interventions for childhood tinnitus and/or hyperacusis. Currently, we have no national established tinnitus clinic for this population group in Denmark. A study of referral patterns and interventions that I conducted during my PhD indicated a general uncertainty about which services provide acquire sufficient interventions due to the structure of the Danish health care system, and children were identified and referred by chance. The intervention study will focus on developing a special service with critical mass for those children with tinnitus and/or hyperacusis to an extent that requires intervention.

What aspect of your work personally gives you the

greatest satisfaction?

When I'm able to help connecting people with tinnitus with themselves. After university, I became an examined body psychotherapist. Body psychotherapy is based on the concept that people experience the world not only through their thoughts and emotions but also simultaneously through their bodies. Working with this holistic approach to treatment to address concerns of mind and body as one along with my audiological foundation is very satisfying.

How has your clinical experience influenced your research?

In many ways. I would never had started with research if I hadn't met children and their families struggling with tinnitus. And I would never have had the nerve to start doing research at the age of 42 years old, if I didn't have the sufficient clinical ballast.

What research topic or question currently excites you?

The pathology behind tinnitus is an interesting topic. Are there really structural abnormalities in the hearing system in children with tinnitus? Is it related to hair-cells, the auditory nerve or something else? Is it really an aspect of auditory neuropathy that we see in children or is it possible that the phenomenon of auditory neuropathy is related to the animal research only and not to human research *per se*. Also the risk of noise-induced tinnitus and hearing loss in adolescents due to hours of listening to high levels of music is an important research topic. What is the most useful advice we can give young people, and how do we address it for them in a meaningful way?

What is your favourite piece of clinical research that has been done by others?

I'm very fond of the study by Formby and colleagues [1] in which they evaluated predictions that followed directly from theoretical assumptions about the role of the gain mechanism in the control of hyperacusis and its treatment. They found that subjects who used earplugs showed increased judged loudness for sounds, whereas subjects who listened to a low-level wideband noise showed decreased judged loudness, which were consistent with the predictions outlined. This study is easy to explain and understand, and I often refer to it in clinical practice.

What do you think is the biggest challenge facing tinnitus research at the moment?

To design research studies that both provide knowledge that can make us move forward in tinnitus research and can be useful in clinical practice. Also to demonstrate if intervention works or especially if it is possible to show which part of an intervention is more successful. There are so many opportunities for interventions out there, but the evidence is limited.

What are the challenges of translating current research into clinical practice?

Time and awareness. Each time you expand your clinical practice, you need to add new procedures, new habits and you have to experiment in exactly how you can translate the research into your practice.

What aspect of research gives you the most hope for future treatments for tinnitus?

A better understanding of how the brain works will also give something to the treatment of tinnitus. It could be related to better understanding of auditory neuropathy in humans. Is it related to noise exposure and can it also explain tinnitus in normal hearing individuals?

Is there any advice you would give to others considering a research path in tinnitus alongside (or from) a clinical career?

Don't be afraid to ask for help and guidance, and be kind and helpful to others. Embrace both the clinician and the researcher inside you and remember to have patience with yourself. It is a process to develop a research path in tinnitus alongside a clinical career, but both working with people with tinnitus is so giving, so remember also to enjoy the journey.

Thank you Susanne. It sounds as though you yourself have had a very enjoyable journey into the research field.

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PROFESSOR DAVID BAGULEY
Professor in Sciences / Deputy Director
University of Nottingham / NIHR Nottingham Biomedical Research Centre

David Baguley is a Professor of Hearing Sciences at the University of Nottingham, working in the Division of Clinical Neurosciences (Faculty of Medicine), and the Otology and Hearing Group. He heads up the Clinical Hearing Sciences group within the NIHR Biomedical Research Centre. David's particular research interests lie in the area of iatrogenic tinnitus and hearing loss associated with the use of platinum-based chemotherapy in adult survivors of cancer.

For over 30 years David was the Head of Audiology at Cambridge University Hospitals NHS Foundation Trust, an in the last 5 years the Head of Auditory Implants and of Newborn Hearing Screening also.

David has co-authored over 150 research papers, many book chapters, and has co-authored and edited several books.He has twice been awarded the Shapiro Research Prize of the British Tinnitus Association, and in 2006 received an International Award in Hearing from the American Academy of Audiology.

HYPERACUSIS AND MISOPHONIA

Professor David Baguley

Hyperacusis (also described as decreased, reduced, or collapsed sound tolerance) is a symptom that is attracting an increasing amount of interest, both clinical and research. Rather than describing extraordinarily sensitive hearing, like Superman being able to hear a whisper 200 metres away, hyperacusis is the experience of the world of sound becoming overwhelmingly intense, such that sound of even moderate intensity is perceived as hyper-intense, and in some cases, painful. Sub-categories of hyperacusis have been proposed [1], wherein it may be characterised by pain, loudness or fear: like all such frameworks there are issues with this, as the categories are not mutually exclusive, but the idea that emotion, auditory perception, and physical discomfort can be interwoven is compelling.

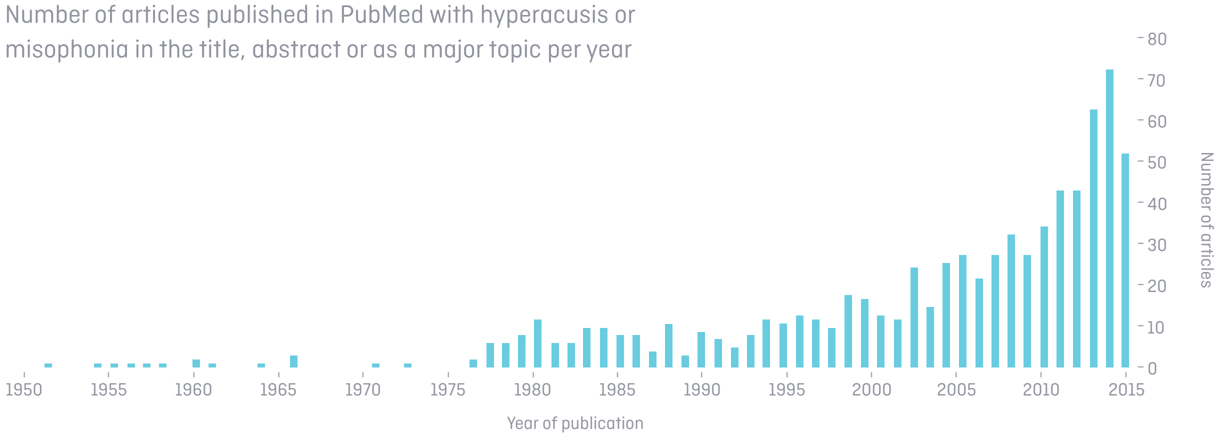
Misophonia is a different experience, though time will tell if there are similarities in the neurobiology of misophonia and hyperacusis. A person with misophonia will exhibit marked aversion to certain sounds, and the characteristic experience is of distress and disgust at the sound of family members eating. This is more common in adolescents and young adults, and can lead to major family tensions, with anger and rage being typical emotional reaction from the patient.

The growth of research activity in the fields is illustrated by Figure 1, in which the numbers of papers published each year with *hyperacusis* and *misophonia* as a keyword is indicated. Whilst unanswered questions regarding each condition abound, the increase in published research is encouraging as clinicians and researchers start to engage these experiences with serious intent, taking steps towards understanding, and eventually, truly effective treatments.

In this section of the Research Report the research published in 2016 on hyperacusis, and on misophonia is reviewed. Regarding hyperacusis alone, as the following analyisis would not be meaningful for misophonia given the small number of papers,

Figure 1

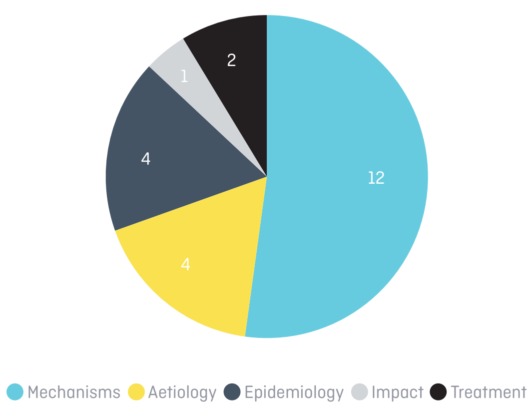
Number of articles published in PubMed with hyperacusis or misophonia in the title, abstract or as a major topic per year



a thematic analysis was performed. PubMed searching identified 43 papers on hyperacusis, and of these 26 were deemed to have a sufficient focus on decreased sound tolerance to be reviewed here. Figure 2 shows the numbers by the themes of mechanisms, aetiology, epidemiology, impact, and treatment. An interesting, and somewhat unexpected finding was that research attempting to identify mechanisms of hyperacusis was the frontrunner, although understanding the pathophysiology of the condition is an essential precursive step to understanding the natural history, and then the design of clinically and cost effective treatment and interventions. These themes will now be used as a framework within which to reflect upon research in 2016.

Figure 2

Number of articles published in PubMed with hyperacusis as a major focus, by theme



Mechanisms

Hidden hearing loss is a term that refers to a recently identified situation which can follow noise exposure, and may also be an early indicator of age-related hearing loss. For many years it was considered that the inner ear structures most vulnerable to noise, and to ageing, were hair cells, but attention has now turned to the synapses (neural connections) between the hair cells instead. It has been proposed that if these degenerate with age, or are damaged by noise, then hearing thresholds would not change – but that the ability to discriminate sound in background noise, and to perceive and tolerate loudness would deteriorate, changes in thresholds then following over time and further damage/ degeneration. This phenomenon has been studied in animals [2], using a drug (carboplatin) that affects these synapses and this is of interest as this drug is used in some cancer treatments in humans. In a study involving humans, Liberman *et al* compared two groups of college students [3]. Both groups had normal hearing on pure tone audiometry on the usual frequencies tested (250Hz-8kHz), but one group had been exposed to very little noise, whilst the other had considerable noise exposure, and hence was at higher risk of hidden hearing loss (synaptic dysfunction/damage). The high risk group had hearing loss on high frequency audiometric testing (10-16kHz), poorer performance on word recognition tests in noise or with degraded speech, and abnormal findings on a diagnostic test of cochlear function (electrocochleography).

The authors inferred that this test battery has potential value in the diagnosis of hidden hearing loss, and that hidden hearing loss may explain why some people had difficulty hearing in noisy situations. Liberman and colleagues also suggested that this synaptic damage may be one of a number of physiological contributors to the onset of tinnitus and/or hyperacusis. Niwa and colleagues noted that similar physiological patterns to that seen in hidden hearing loss were observed after blast injuries in rats [4], and also wondered if this might contribute to hyperacusis and tinnitus.

An alternate, though not necessarily contradictory, view about people exposed to loud sound who retain normal audiograms but who struggle to discriminate sound in background noise was proposed by Eggermont [5]. His perspective was on changes in the central auditory system (e.g. brain structures and networks involved in hearing), describing alterations in central gain (the way that the brain boosts quiet sound) and the frequency maps for sound in the cortex, which is where sound is analysed and interpreted. Such changes have long been associated with hyperacusis and tinnitus, and this promises to be a fruitful area for further research.

Longer term effects of noise exposure were investigated by a number of researchers. Clarkson and colleagues [6] considered the effects on the auditory brain of conductive hearing loss in rats. Such losses are common in human children with otitis media with effusion (glue ear), and so this is a topic of some interest. Clarkson and colleagues indicated that there were substantial adverse changes, including some that might lead to decreased sound tolerance, although they did not research any eventual recovery or remediation of those effects. Turner and Larsen [7] explored changes in the auditory behaviour of rats 12 months after intense sound stimulation, considering both tinnitus and hyperacusis, though this work focused more heavily on tinnitus than decreased sound tolerance.

A number of other themes regarding the mechanisms of hyperacusis were explored in 2016. Researchers in Nottingham [8] and New York [9] investigated the effects of large doses of salicylate (aspirin) in animals, which has previously been reported to induce tinnitus and/or hyperacusis, but a research group in Cleveland [10] reported results demonstrating how difficult it is to disentangle any possible experimentally induced tinnitus in an animal from any hyperacusis. This challenge was also the topic of a study by Knudson and Melcher [11] whose results indicate that the auditory startle response (ASR) in humans may not correspond to self-reported sound tolerance challenges, and hence question whether ASR can be used as a marker for hyperacusis in animal models.

Encouragingly, a variety of different perspectives are starting to be explored. The association between autism and sound tolerance issues has long been noted, though little empirical evidence has been gathered, but physiological research is next to non-existent. A group of Japanese researchers [12] has begun to research sound sensitivity in a rat model of autism: their initial work indicates a potential failure of inhibitory progressing within the auditory brain. Discussion about mechanisms of sound-induced pain arose in work by Manohar *et al* [13], again drawing parallels between brain changes after noise induced hearing loss, and chronic pain signals.

Aetiology

Aetiology is the cause or causes of a disease or condition. When it comes to hyperacusis, many and multiple aetiologies have been proposed, and researchers are vigilant in this area. Viziano *et al* [14] investigated decreased sound tolerance in patients with Multiple Chemical Sensitivity (MCS), which is a chronic condition resulting from low-level chemical exposure. Audiometric thresholds and a measure of cochlear function were normal in the 18 patients studied, but self-report measures of sound tolerance were indicative of hyperacusis, and the authors proposed that this may be a central phenomenon. Fioretti *et al* [15] published a case report of a patient in whom hyperacusis was associated with photophobia, and with skin hypersensitivity: treatment with sound therapy, cognitive behaviour therapy, and with an antidepressant led to improvements in mood, and in the ability to tolerate both sound and light. Another case study [16] proposed that certain genetic variations found in a young female patient with autism may have been associated with her sensory sensitivities: whilst of interest, this is an emergent field of research. Degeest *et al* [17] presented questionnaire data from a series of 81 patients with troublesome tinnitus, indicating that the presence and extent of hyperacusis contributed to the self-reported handicap in this series, which fits clinical observations. Whilst each of these different perspectives is of interest, research on the causes of hyperacusis did not make substantial progress in 2016.

Epidemiology

Research into the prevalence, incidence, characteristics and natural history of disorders of decreased sound tolerance is extremely important in building our understanding of these symptoms and formulating effective treatment interventions. Knowledge and data regarding the epidemiology of hyperacusis is sparse, and there has been some research activity in this area published in 2016.

In a large scale general population questionnaire study from Sweden, Paulin *et al* [18] found that of 3374 adult individuals who responded to the study invitation, 313 self-reported as having hyperacusis (9.3%), and 66 (2.0%) had been diagnosed with hyperacusis by a physician. Factors associated with hyperacusis included higher age, female gender, and higher educational status, and other medical conditions co-incident with hyperacusis included tinnitus, post-traumatic stress, chronic fatigue, pain syndromes, and hearing loss. Whilst not breaking new ground, this work does substantiate and build upon previous studies.

A systematic review [19] of tinnitus and hyperacusis in children and adolescents concluded that the data available contained so many methodological challenges that little in the way of firm evidence could be gleaned. Variability of definitions, questions asked, and populations studied with regard to age and hearing status, rendered comparison across studies meaningless. Studies published subsequently on tinnitus [20] and hyperacusis [21] on a cohort of approximately 7000 11 year olds in the UK indicated that 3.5% of the cohort experienced tinnitus that was persistent and bothersome, and that 3.7% reported hyperacusis. The report of hyperacusis was associated with female gender, higher maternal educational level, and readmission to hospital in the first 4 weeks of life. It has previously been noted that far fewer children with tinnitus and hyperacusis are seen in clinical practice than are detected by population studies, and Rosing *et al* [22] indicated that very few children with tinnitus and/or hyperacusis are seen in clinics in Denmark, and those that are referred are in general seen in clinics primarily treating adults.

Impact

Only one research paper published in 2016 considered the impact of hyperacusis, and that investigated the impact upon hearing abilities rather that the psychosocial domains. Vielsmeier *et al* [23] researched speech comprehension difficulties in patients with tinnitus, and found that the presence of hyperacusis was associated with poorer test performance in noise, but not in quiet environments. The authors proposed that a deficit in inhibition in the central auditory system might underlie both decreased sound tolerance and poorer speech comprehension in noise.

Treatment

The effectiveness of treatments for tinnitus and hyperacusis in the UK NHS were assessed by Aazh and colleagues [24]. Talking therapies were rated most highly, and sound therapies relatively lowly. There are a number of learning points here: first, that the opinion of patients about their treatment is highly important. Second, that is a substantial challenge to disentangle the effects of tinnitus and hyperacusis in research studies. Finally, this corroborates the view that sound therapies for both hyperacusis and tinnitus remain underdeveloped and under-evaluated, and there are some major opportunities in this area.

Silverstein *et al* [25]reported the results of a surgical procedure for severe intractable hyperacusis that had been unresponsive to other therapy. Both the round and oval window of the cochlea were reinforced with other membranes in six patients (nine ears), and modest improvements on loudness discomfort testing was reported, alongside some improvement on questionnaire data. This observational study, though prospective, does not carry the same weight as a randomised controlled trial. Additionally, if the view that decreased sound tolerance is associated by increased central auditory gain has validity, then the same concerns about a surgical procedure that reduces auditory input to the cochlea would apply as do to the long term chronic use of hearing protection in hyperacusis.

Misophonia

Surprisingly, given the amount of discussion about misophonia amongst audiologists and patient groups, only one research paper was published. Bruxner *et al* [26] present a case report and a review, coming from the perspective that misophonia is an under recognised psychiatric symptom, and giving it the sobriquet “mastication rage”. The debate about whether misophonia is essentially an audiological or a psychological disorder, or both, has further ground to cover, as does the quest for effective clinical interventions.

Discussion

Whilst it is encouraging that the research literature regarding hyperacusis is growing, and emanating from a number of different disciplines, there are a number of concerns. In 2016 a number of themes were entirely lacking, for example measurement and questionnaires, and natural history. The literature that does exist is often very specific, and potentially more concerned with the interests and concerns of the researcher/clinician rather than the patient community. In this latter regard the excellent work of Hyperacusis Research (www.hyperacusisresearch.org) should bear fruit in bring patient concerns to the forefront of research, and in providing a framework wherein researcher and clinicians can work together in a co-ordinated and comprehensive body of research.

The views expressed in this publication are those of the author(s) and not necessarily those of the National Institutes of Health, the National Institute for Health Research, or the Department of Health.

Conflict of interest:
David Baguley was an author on four of the papers mentioned herein. He is an Editor with Prof Marc Fagelson of a forthcoming book on hyperacusis, published by Plural Publishers in Autumn 2017.

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