



Research paper

History of the Tinnitus Research Consortium

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ARTICLE INFO

Article history:

Received 2 June 2015

Accepted 5 June 2015

Available online 19 June 2015

Keywords:

Tinnitus
Research
Consortium

ABSTRACT

This article describes the creation and accomplishments of the Tinnitus Research Consortium (TRC), founded and supported through philanthropy and intended to enrich the field of tinnitus research. Bringing together a group of distinguished auditory researchers, most of whom were not involved in tinnitus research, over the fifteen years of its life it developed novel research approaches and recruited a number of new investigators into the field. The purpose of this special issue is to highlight some of the significant accomplishments of the investigators supported by the TRC.

This article is part of a Special Issue entitled "Tinnitus".

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1. Introduction

Richard G. Schneidman, accountant to the Robert W. Wilson Charitable Trust, contacted me in May 1998 to inquire if I would be willing to manage an effort to accelerate research on tinnitus directed at a cure. Refreshed by living on the Eastern Shore of Maryland after retiring in 1997 from the directorship of the National Institute on Deafness and Other Communication Disorders (NIDCD) at the National Institutes of Health (NIH), I agreed to develop a research-grant plan to improve and accelerate tinnitus research for presentation to Mr. Wilson at his home in New York.

2. Research plan

The plan featured the creation of the Tinnitus Research Consortium (TRC) which was to be composed of 12 distinguished auditory scientists some of whom had worked in tinnitus research and others who had not. The TRC would guide the research-grant program by evaluating the status of basic and clinical tinnitus

research, determine the reasons for characteristically slow progress in the field, recommend worthy initiatives, develop requests for applications (RFAs), evaluate the applications received, review the grantees' progress and suggest to the grantees ways in which their research could be made more valid and productive (Snow, 2013). Current members of the TRC are Drs. William E. Brownell, Donald M. Caspary, Robert A. Dobie, Judy R. Dubno, Pawel J. Jastreboff, M. Charles Liberman, Brenda L. Lonsbury-Martin, Alfred L. Nuttall, Allen F. Ryan, Robert V. Shannon, Christoph E. Schreiner and P. Ashley Wackym. Former members include Richard A. Chole, Peter Dallos, Bruce J. Gantz, A. James Hudspeth and Leonard P. Rybak.

The first decision made was regarding the amount and duration of the grants. It was determined that the grants-in-aid would provide up to \$100,000.00/annum over a three-year period so they would be large and long enough to support a substantial research project. This decision has encouraged several other voluntary agencies to increase the amount and duration of their support of tinnitus and other research toward the TRC standard. Typically, during the last 15 years, two awards were made each year, however in 2011 the available funds were increased to allow three awards each year. Over the 15-year period, the direct costs of the program exceeded eight million dollars. Furthermore, during this period, the NIDCD and other institutes at the NIH have devoted more emphasis to tinnitus as has the Department of Defense.

3. Meetings of the Tinnitus Research Consortium

In the semiannual TRC meetings, the brainstorming for new research approaches to tinnitus included reviews of basic and clinical research to identify the next logical steps. With experience,

Abbreviations: NIDCD, National Institute on Deafness and Other Communication Disorders; NIH, National Institutes of Health; TRC, Tinnitus Research Consortium; RFAs, request for applications; TFI, Tinnitus Functional Index; GPIAS, gap pre-pulse inhibition of the acoustic startle; IC, inferior colliculus; OAEs, otoacoustic emissions; BDP, binaural difference potential; VCN, ventral cochlear nucleus; DCN, dorsal cochlear nucleus; BBN, broad band noise; RF, reticular formation; CN, cochlear nucleus; NIHL, noise induced hearing loss; GPIASR, gap pre-pulse inhibition of the acoustic startle reflex; tph2, tryptophan hydroxylase; TRT, tinnitus retraining therapy

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the TRC began to articulate the common confounding variables in tinnitus research and to develop RFAs that not only elicit the research to be accomplished but suggested solutions to the identified roadblocks. In this process, the Members of the TRC recognized and bought into the intellectual challenge posed by research on tinnitus.

Initially, the TRC was uncertain of the validity of the existing behavioral models of tinnitus whereas there had been clinical trials of treatment for tinnitus judged to be scientifically meritorious. Therefore, the first two RFAs for grants-in-aid to be funded by the TRC were for clinical trials, one on electrical stimulation of the auditory system for the suppression of tinnitus and the other on the management of patients with tinnitus with selective serotonin reuptake inhibitor antidepressants. Two awards were made in 2000, one for each RFA. The clinical trial of electrical stimulation was performed by Dr. Jay T. Rubinstein and his group at the University of Iowa and involved application of the stimulus to the inner ear through the middle ear or through a cochlear implant. They demonstrated for the first time that high-rate electrical pulses (5000/s) can suppress tinnitus without producing an audible percept (Rubinstein et al., 2003).

Drs. Murray B. Stein and Shannon K. Robinson at the University of California, San Diego studied the serotonin reuptake inhibitor antidepressant paroxetine in individuals with bothersome tinnitus who did not have depression. An antidepressant drug of a different type had appeared to be more effective in individuals with tinnitus and insomnia or depression, and Stein and Robinson's subjects did not significantly benefit from the use of paroxetine (Robinson et al., 2005). This well designed and executed clinical trial continues to guide the field.

4. Consultation with other experts

In a strategy used more than once by the TRC, the issue of the validity of the existing animal models of tinnitus was addressed by assembling foremost experts in behavioral animal models who had not worked in tinnitus research in the past to analyze the validity of these models. The conclusion of the TRC after this consultation was that several existing animal models of tinnitus were scientifically sound, however additional animal models of tinnitus should be developed. Therefore, the TRC issued an RFA for development and validation of new animal models of tinnitus. Parenthetically, two of these experts became so engaged in the intellectual challenge at hand that they applied for and received TRC grants to develop a better animal model of tinnitus.

Over the years, the following consultants have made presentations to the TRC and participated in some of its brainstorming sessions: in 2000, Peter A. Cariani at Harvard Medical School and the Eaton Peabody Laboratory of the Massachusetts Eye and Ear Infirmary spoke on *How Does Neural Coding Become Auditory Perception? New Coding Issues in Understanding Tinnitus*; in 2001, Josef P. Rauschecker at Georgetown University spoke on *Tinnitus as a Phantom Sensation – New Vistas in Functional Organization of the Auditory Cortex*; in 2003, Howard J. Hoffman, Director of the Epidemiology and Statistics Branch of the NIDCD, spoke on the *Epidemiology and Genetics of Tinnitus*; in 2007, Joseph E. LeDoux at New York University spoke on *How the Brain Processes Emotion and Fear and How Studies of Emotion and Fear Could Be Relevant to Tinnitus*; also in 2007, John F. Disterhoff at Northwestern University spoke on *Cellular System Mechanisms of Associative Learning in the Young and Aging Brain – Potential Relevance to Understanding Tinnitus*; in 2008, Shihab A. Shamma at the University of Maryland spoke on *Influence of Behavior on Auditory Cortical Responses*; in 2010, Jos J. Eggermont at the University of Calgary spoke on the *Role of Cortical Synchrony in Tinnitus*; and in 2011, Steven W. Cheung at

the University of California, San Francisco spoke on *Modulation of Tinnitus with Stimulation of the Caudate Nucleus*. The intellectual contribution of these individuals to the work of the TRC has been enormous.

5. Tinnitus Functional Index

In analyzing the clinical research on tinnitus, it became apparent to the TRC that it was difficult to compare the outcome of similar studies because of the lack of uniform measurement of the outcomes. It was generally agreed that the use of patient questionnaires was the proper way to determine outcome in tinnitus in view of its subjective nature, but the problems were the lack of uniformity in and adequacy of the measurement instruments. These problems were particularly apparent in the comparison of clinical trials because of the large number of patient questionnaires used in these studies. Furthermore, the available questionnaires had not generally been validated by modern standards. With advice from experts on outcome measures, the TRC came to the conclusion that an improved outcome measure should be developed to serve as a universal standard.

In 2003, an RFA was issued for the development and evaluation of a new outcome measure for tinnitus, and an award was made to the late Dr. Mary B. Meikle at Oregon Health and Science University in 2004 to develop and validate the Tinnitus Functional Index (TFI). She and her outstanding team have brought forth an outcome measure of tinnitus that provides comprehensive coverage of the factors important in determination of the severity of tinnitus and has strong validity and high responsiveness to treatment-related change (Meikle et al., 2012). It is anticipated that the 25-item TFI will become the English language standard for measurement of tinnitus in research as well as clinical practice.

Translation of the questionnaire into other languages requires linguistic (semantic and conceptual) equivalence and cultural adaptation. Some authorities on translation and cultural adaptation of patient outcome measure questionnaires recommend procedures to forward translate, reconcile the forward translations, back translate and compare back translations with the original although data supporting these recommendations are not available.

The procedures include the following: forward translation from the source language to the target language by at least two independent native speakers of the target language familiar with the content of the source material; reconciliation or comparing and merging of more than one forward translation into a single forward translation by the translators; back translation of the new language version by at least two independent native speakers of the source language into the source language; and review of the back translations to compare back translated versions with the original to identify discrepancies in meaning or concept.

Following the translation and assurance of its cultural adaptation, the determination of the reliability, validity and responsiveness of each item and the questionnaire as a whole should be carried out in individuals who are native speakers of the target language who have bothersome tinnitus.

6. Other landmark projects

Other landmark studies supported by the TRC that have changed the conceptualization of the pathogenesis of tinnitus and its management can be categorized under the following headings: imaging tinnitus-related activity in the central nervous system; the role of the somatosensory system in the generation and modification of tinnitus; identification of the neural networks associated with tinnitus and their interaction with the limbic and other systems

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