BIOGRAPHICAL SKETCH

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NAME: Jinsheng Zhang

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POSITION TITLE: Professor and Research Director

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Hebei Normal University, China	BS	1981-1985	Biology
Hebei Normal University, China	MS	1985-1988	Physiology
University of Fribourg, Switzerland	PhD	1994-1997	Neurophysiology (Advisor, Eric Rouiller)
Wayne State University, USA	Postdoctoral	1997-2000	Auditory Neuroscience (Advisor, J. Kaltenbach)
Wayne State University, USA	MS courses	1998-2001	Electronics & Computer Control System

A. Personal Statement

My background has been investigating the mechanisms of trauma (noise, blast, and concussion)-induced tinnitus and related traumatic brain injury (TBI) through behavior assays, *in vivo* multichannel and multi-structural electrophysiology, MRI and MEMRI imaging and immunocytochemistry, modulating tinnitus through electrical, chemical and optogenetic stimulation via auditory and limbic brain implants, drug development for treating tinnitus and TBI, and developing cochlear and brain implantable devices. During my Ph.D. training, I characterized neural activation along the auditory pathways following cochlear electrical stimulation using a rat model of cochlear implants (a). During my postdoctoral training, I investigated noise-induced hyperactivity in the dorsal cochlear nucleus and other auditory and non-auditory centers and their relationship to tinnitus (b). Since then, I have developed multi-structural recordings from both auditory and non-auditory centers including the amygdala in rats. This approach allows for the investigation of how neural network within and across different centers contributes to the etiology of tinnitus. I demonstrated that electrical stimulation of the dorsal cochlear nucleus not only induces hearing (c) but also suppresses tinnitus in a rat model (d). I investigated the biocompatibility of implantable materials by evaluating electrophysiology, astrocyte reactivity, and gene expression. I collaborate with engineers and clinicians to develop advanced analytical tools for signal processing and new generation multi-channel implantable devices for brain stimulation and management of tinnitus, TBI and other neurological disorders.

a) *Zhang, J.S., Haenggeli, A., Tempini, A., Vischer, M.W., Moret, V. and Rouiller, E.M. (1996) Electrically induced Fos-like immunoreactivity (FLI) in the auditory pathway of the rats: effects of survival time, duration and intensity of stimulation. Brain Res. Bullet., 39 (2): 75-82.*

b) *Zhang, J.S. and Kaltenbach, J.A. (1998) Increases in spontaneous activity in the dorsal cochlear nucleus of the rat following exposure to high intensity sound. Neurosci. lett., 250: 197-200.*

c) *Zhang, J.S, Zhang, X.G. (2010) Electrical stimulation of the dorsal cochlear nucleus induces hearing in rats. Brain Res. 1311:37-50.*

d) *Luo, H., Zhang, X.G. Nation, J. Pace, E., Lepczyk, L. and Zhang, J.S. (2012) Tinnitus Suppression by Electrical Stimulation of the Rat Dorsal Cochlear Nucleus. Neurosci Lett. 522:16-20.*

B. Positions and Honors

Positions and Employment

1988-1990 Teaching Assistant, Department of Biology, Hebei Normal University, China
1990-1993 Lecturer, Department of Biology, Hebei Normal University, Shijiazhuang, China

2000-2005	Assistant Professor, Dept of Otolaryngology, Wayne State University School of Medicine
2005-2012	Associate Professor, Dept of Otolaryngology, Wayne State University School of Medicine
2006-2012	Associate Professor, Department of Communication Sciences and Disorders, Wayne State University College of Liberal Arts and Sciences
2012-present	Professor, Department of Otolaryngology, Wayne State University School of Medicine
2012-present	Professor, Department of Communication Sciences and Disorders, Wayne State University College of Liberal Arts and Sciences

Other Experience and Professional Memberships

1997-present	Member, Association for Research in Otolaryngology (ARO)
2000-present	Member, American Tinnitus Association (ATA)
2002-present	Member, Society for Neuroscience (SFN)
2004-present	RNID grant Reviewer, Royal National Institute for Deaf people (UK)
2006	Co-chair, Podium session, ARO MidWinter Meeting, Maryland
2006-2007	Director, Basic Science Course, Department of Otolaryngology, Wayne State University
2006-present	Ex-Officio Board Member, Lions Hearing Institute of Michigan
2007-present	Research Director, Department of Otolaryngology, Wayne State University School of Medicine
2008-present	DOD Panelist, Department of Defense **-** Congressionally Directed Medical Research Program grant review panel – Peer Reviewed Medical Research Program (PRMRP)
2011-present	MRC Grant Reviewer. Neurosciences and Mental Health section, Medical Res Council (UK)
2012-present	Associate Chair for Research, Dept Otolaryngology, Wayne State Univ School of Medicine
2010-2014	ATA Scientific Advisory Committee, American Tinnitus Association
2012-2014	ITS Scientific Committee, XI International Tinnitus Seminar, Berlin, Germany
2013-present	VA grant reviewer, Department of Veterans Affairs
2013-2016	ARO External Relations Committee
2013	TRI Panel Chair. The 7th International TRI Conference on tinnitus. May 15-18, 2013
2014-2015	Scientific Advisory Committee, The 9th TRI International Tinnitus Conference – Tinnitus from Cochlea to Brain and Back. Ann Arbor, USA
2014-2015	Editor, Special Issue in Frontiers in Neurology - Tinnitus: An Attempt to Confront the Diverse Models. http://www.frontiersin.org/neuro-otology/researchtopics/Tinnitus_an_attempt_to_confron/2633
2015-2017	Board of Directors, The American Tinnitus Association (ATA). July 1, 2015-June 30th, 2017.
2015-2017	Chair, Scientific Advisory Committee, The American Tinnitus Association (ATA).

Honors

1994	Award of Excellence in Scientific Research and Teaching, Hebei Normal University
1994-1997	Fellowship Award of Swiss National Foundation for Scientific Research (FNRS)
1997	Award of Excellent Scholar: Dept of Education, the Embassy of P.R. China to Switzerland
2001-present	Honorary Professor, School of Life Sciences, Hebei Normal University
2008	WSU President's Translational Research Enhancement Program Award on development of brain implants and stimulation
2010	Nominee of WSU 2011 President Award of Excellence in Teaching
2011	Recipient of President's Research Enhancement Program Award on tinnitus diagnosis and treatment technology development.

C. Contributions to Science

1. Cochlear electrical stimulation-induced neural activation along the auditory pathways.

Cochlear implant is routinely used to restore hearing for the profoundly deaf people. We used a cochlear implant animal model and multidisciplinary techniques to investigate how the cochlear implant functions by recording cochlear stimulation-induced neural activation along the auditory pathway. We found that cochlear electrical stimulation at low rates generates high amplitude of the electrically evoked compound action potentials (ECAP) in the auditory nerve, whereas at high rate of stimulation, the amplitude of the ECAP decreases. In spite of this decreased number of auditory nerve fibers stimulated at high rates, the major advantage of high rate stimulation is to allow a better representation of the rapid temporal changes present in the speech signals, which appears to be the crucial factor for better speech recognition in patients using CIS strategy (Wilson et al. 1991), possibly mimicking more closely the activity generated by an acoustic stimulus. This indicates that our animal model of cochlear implants is appropriate to study clinically relevant issue (a,b). In single unit recording from the central nucleus of the inferior colliculus (CIC) with one ear stimulated

electrically and another stimulated acoustically, we found that a large proportions of CIC neurons were activated by electrical stimulation, comparable to that in response to acoustic stimulation, e.g., 90% for contralateral and 60% for ipsilateral presentation. With respect to binaural inputs, the majority of units were excited by stimulation of either ear (EE: about 60%) while about one third were influenced by one ear only (EO). Units excited by one ear and inhibited by the other (EI) were rare, indicating the possible plastic changes resulting from implantation of the electrodes or repeated electrical stimulation (c). To study a larger population of neurons with cellular resolution, we used *c-fos* immunocytochemistry in which the proto-oncogene *c-fos* is expressed following a great variety of internal and external stimulation. We found that C-fos induction in the auditory pathway following cochlear electrical stimulation, which varies with stimulation parameters (d).

a) *Zhang, J.S., Vischer, M.W., Haenggeli, C.A. and Rouiller, E.M. (1997) Responses of the auditory nerve to high rate pulsatile electrical stimulation: comparison between normal and deafened rats, Chapter 53, In: Acoustical Signal Processing in the Central Auditory System, Syka, J. (Ed.), Plenum Press, New York, pp. 577-583.*
b) *Haenggeli, A., Zhang, J.S., Vischer, M.W., Pelizzone, M. and Rouiller, E.M. (1998) Electrically evoked compound action potential (ECAP) of the cochlear nerve in response to pulsatile electrical stimulation of the cochlea in the rat: effects of stimulation at high rates. Audiology, 37: 353-371.*
c) *Vischer, M.W., Bajo, V., Zhang, J.S., Calciati, E., Haenggeli A. and Rouiller, E.M. (1997) Single unit activity in the inferior colliculus of the rat elicited by electrical stimulation of the cochlea. Audiology, 36: 202-227.*
d) *Zhang, J.S., Haenggeli, A., Tempini, A., Vischer, M.W., Moret, V. and Rouiller, E.M. (1996) Electrically induced Fos-like immunoreactivity (FLI) in the auditory pathway of the rats: effects of survival time, duration and intensity of stimulation. Brain Res. Bullet., 39 (2): 75-82.*

2. Noise-induced tinnitus and its underlying neural mechanisms and behavioral evaluation

Noise-induced tinnitus is a prevalent health problem. To search for the neural mechanisms underlying tinnitus, we found that intense noise exposure causes increased spontaneous firing in the dorsal cochlear nucleus (DCN) (a). We also found that the noise-induced hyperactivity in the DCN is closely related to the strength of behavioral evidence of tinnitus. This indicates that the induced DCN hyperactivity may represent the neural mechanism of tinnitus. In addition to noise exposure, we found other ototoxic agents such as cisplatin also found causes hyperactivity in the DCN. The induced hyperactivity in the DCN was initially broadly distributed and then shifted towards the high-frequency region in the DCN, demonstrating active and complex plastic process. In cochlear ablation and DCN, we found that noise-induced DCN hyperactivity is of central original. In a circumscribed sectioning study attempting to cut off inputs to the DCN, we found that the induced hyperactivity is intrinsic to the DCN and can be affected by descending inputs (b). We also used *c-fos* immunocytochemistry and found that neural correlates of tinnitus exist in both auditory and non-auditory structures. The auditory structures included the lateral leminiscus, central nucleus of the inferior colliculus and auditory cortex. The non-auditory structures included the locus coeruleus, lateral parabrachial nucleus, certain subregions of the hypothalamus and amygdala. In improve behavioral testing of noise-induced tinnitus, we recently optimized a behavioral paradigm for testing tinnitus by applying statistical method (c). We also found that tinnitus does not always result in cognitive emotional dysfunctions, although tinnitus may predispose subjects to anxiety (c). Recently, we developed a conditioned-licking paradigm to test for behavioral evidence of tinnitus (d), to more reliably test tinnitus.

a) *Zhang, J.S. and Kaltenbach, J.A. (1998) Increases in spontaneous activity in the dorsal cochlear nucleus of the rat following exposure to high intensity sound. Neurosci. lett., 250: 197-200.*
b) *Zhang, J.S., Kaltenbach, J.A., Godfrey, D.A. and Wang, J. (2006) Origin of hyperactivity in the hamster dorsal cochlear nucleus following intense sound exposure. J. Neurosci. Res., 84:819-831.*
c) *Pace, E. and Zhang, J.S. (2013) Noise-Induced Tinnitus Using Individualized Gap Detection Analysis and Its Relationship with Hyperacusis, Anxiety, and Spatial Cognition. PloS ONE 8(9): e75011*
d) *Zhang, J.S., Luo, H., Pace, Ed. And Liu B. (2015) Neural Correlates of Noised-Induced Tinnitus in Animals: Intra-and Inter-Auditory and Non-Auditory Brain Activity Studies. Hearing Res. doi:10.1016/j.heares.2015.08.006.*

3. Blast-induced tinnitus, its underlying neural mechanisms and treatment

Among the many forms of acoustic exposures, blast, a high-energy impulse noise, has received significant attention due to the large number of injured soldiers. Blast can induce a wide range of pathologies in the body, including auditory pathology such as tinnitus and hearing loss, as well as traumatic brain injury (TBI). However, there is no effective treatment for blast-induced tinnitus and its related TBI, mainly due to an unclear understanding of its underlying mechanisms. My lab established a rat model of blast-induced tinnitus and

related TBI (a). Behaviorally, we found that blast exposure induces early onset of tinnitus and central hearing impairment (a). The induced tinnitus and central hearing impairment shifts towards high frequencies over time, indicative of neuroplasticity. Diffusion tensor imaging results showed significant damage and compensatory plastic changes to certain auditory brain regions such as the inferior colliculus and medial geniculate body (a). Electrophysiologically, we found that blast exposure induced onset hyperactivity in the DCN and IC of rats with tinnitus (b,c). The induced hyperactivity in the DCN persisted at one month after blast exposure. At three months following blast, the induced hyperactivity transitioned to hypoactivity in the DCN (b). We also found that the induced hyperactivity in the IC persisted at both three and six months after blast trauma (c). The results demonstrated that the mechanisms underlying blast-induced tinnitus are much more different from those underlying noise-induced tinnitus. To seek pharmaceutical treatments, we demonstrated that sildenafil significantly suppressed blast-induced tinnitus from 3 to 6 weeks after blast exposure, as well as showed therapeutic effects on TBI and hyperacusis aspects (d).

a) *Mao, J., Pace, E., Pierozynski, P., Bobak, L., Kou, Z. F., VandeVord, P., Shen, Y.M., Haacke, M., Zhang, X.G., Zhang, J.S. (2012) Blast-induced tinnitus and hearing loss in rats: Behavioral and imaging assays. J. Neurotrauma, 29:430-444.*
b) *Luo, H., Pace, E., Zhang, X. and Zhang, J.S. (2014) Blast Induced Tinnitus and Spontaneous Firing Changes in the Rat Dorsal Cochlear Nucleus. J. Neurosci. Res., 17 JUN 2014 DOI: 10.1002/jnr.23424.*
c) *Hao Luo, Xueguo Zhang, Edward Pace and Jinsheng Zhang (2014) "Blast-Induced Tinnitus and Hearing Loss and Their Related Neural activity Changes in the Rat Inferior Colliculus". Neurosci. Lett., 580:47-51.*
d) *Mahmood, G., Mei, Z.G., Hojjat, H., Pace, P., Kallakuri, S., and Zhang, J.S. (2014) Therapeutic Effect of Sildenafil on Blast-Induced Tinnitus and Auditory Impairment. Neurosci. 269:367-382.*

4. Development of neural implantable devices

Neural probes have made remarkable contributions in fundamental neuroscience researches and treatments of various neural disorders. Nevertheless, despite steady progresses in the past two decades, there still exists a gap between the performance of current neural probes and the requirements of many neurological researches and applications. One highly desirable feature is 3-dimentional high-density electrodes for electrical recording/stimulating with high spatial resolution. It is also worth noting that the communication between most neurons is mainly a chemical process. Thus, effective prostheses may use combined electrical and chemical stimulations synergistically. In collaboration with engineer colleague Prof. Xu, we successfully developed novel 3D neural probes integrated with electrical and chemical interfaces (a,b). Despite significant progresses, the current BMI is still not clinically ready to make real therapeutic impact due to the challenging biocompatibility issue resulting from inflammation, neurodegeneration, mechanical mismatch, and micromotion. We have investigated different design and biocompatibility (c). Very recently, considering the high-impact of optogenetics on neuroscience and neurological disorders including tinnitus, we successfully developed a novel functional 3D neural probe coupled with optical fibers using a hollow parylene tube structure (d). This new development will allow simultaneous recording while optogenetically modulating targeted neurons.

a) *John, J., Li, Y.F., Zhang, J.S., Loeb, J. and Xu, Y. (2011) Microfabrication of 3D neural probes with combined electrical and chemical interfaces. J Micromech. Micoeng., 21:105011 (11pp).*
b) *Kim, E.G., John, J.K., Tu, H., Zheng, Q., Loeb, J., and Zhang, J.S., and Xu, Y. (2013) A hybrid silicon-parylene neural probe with locally flexible regions.*
c) *Ereifej E, Khan S, Newaz G, Zhang J.S., Auner G, VandeVord P. (2011) Characterization of astrocyte reactivity and gene expression on biomaterials for neural electrodes. J. Biomed Mater Res., 99(1):141-150.*
d) *Eric Kim, Hongen Tu, Hao Luo, Bin Liu, Shaowen Bao, Jinsheng Zhang and Yong Xu (2015) 3D silicon neural probe with integrated optical fibers for optogenetic modulation. Lab on a Chip, Royal Society of Chemistry, DOI: 10.1039/C4LC01472C.*

5. Electrical stimulation to suppress tinnitus and its related neural activity

Although numerous tinnitus management methods have been attempted, there is no reliable treatment for tinnitus. Among stimulation strategies, stimulation of the cochlea, cochlear nucleus, auditory cortex, somatosensory structures, vagal nerve and the prefrontal cortex have demonstrated various therapeutic effects. None of them have become accepted treatment to reliably manage tinnitus. Clinically, our team demonstrated that direct electrical stimulation of Heschl's gyrus of patients produces significant suppression of tinnitus though variability exists. To elucidate the underlying mechanisms of top-down and bottom-up neuromodulation-induced tinnitus suppression, we established a rat model. In the top-down approach, we reported that electrical stimulation of the auditory cortex significantly suppressed behavioral evidence of

tinnitus and enhanced hearing detection at the central level (a,b). We observed that electrical stimulation of the auditory cortex tends to down-regulate spontaneous firing in the DCN, IC and *c-fos* immunoreactivity in the amygdala more in noise-exposed animals than controls. In the bottom-up approach, we reported that somatosensory electrical stimulation induces a higher incidence of suppressive (up to 70%) than of excitatory responses during and after stimulation of the DCN. We also showed that somatosensory electrical modulation involves direct pathways via the spinal trigeminal nucleus and indirect pathways via the dorsal raphe nucleus and locus coeruleus (c). We demonstrated that electrical stimulation of the DCN suppresses behavioral evidence of tinnitus, especially at high frequencies (d).

a) *Zhang, J.S., Zhang, Y.P. and Zhang, X.G. (2011) Auditory cortex electrical stimulation suppresses tinnitus in rats. J Assoc Res Otolaryngol. 12(2):185-201.*
b) *Zhang, J.S. (2013) Auditory Cortex Stimulation to Suppress Tinnitus: Mechanisms and Strategies. Hear Res. 295(1-2):38-57.*
c) *Zhang, J.S. and Guan Z.L. (2007) Pathways involved in somatosensory electrical modulation of dorsal cochlear nucleus activity. Brain Res., 1184:121-131.*
d) *Luo, H., Zhang, X.G. Nation, J. Pace, E., Lepczyk, L. and Zhang, J.S. (2012) Tinnitus Suppression by Electrical Stimulation of the Rat Dorsal Cochlear Nucleus. Neurosci Lett. 522:16-20.*