The mechanical potential of ultrasound on nervous tissue

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JASA REFLECTIONS

The *Reflections* series takes a look back on historical articles from *The Journal of the Acoustical Society of America* that have had a significant impact on the science and practice of acoustics.

The mechanical potential of ultrasound on nervous tissue

Article: Physical factors involved in ultrasonically induced changes in living systems: I. Identification of non-temperature effects
Authors: W. J. Fry, V. J. Wulff, D. Tucker, and F. J. Fry
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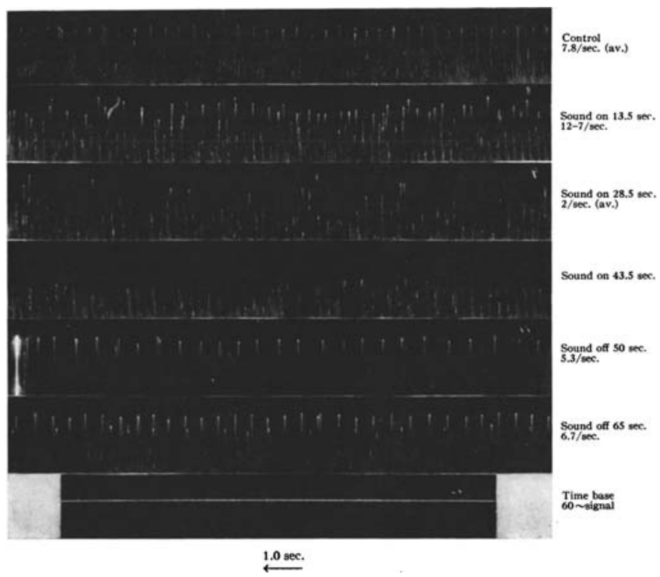
ARTICLE OVERVIEW

In this article, Fry *et al.* provide the first evidence of both reversible and irreversible non-thermal effects of ultrasound in nervous tissue. After first introducing physical principles behind thermal and pressure-related factors in the absence and presence of cavitation, the article goes on to present two key experiments. First, in the excised crayfish ventral nerve, ultrasound is shown to initially increase and then suppress the rate of spontaneous spiking, which is reversible after ultrasound is turned off. The recorded temperature rise of 1 °C is of sufficient magnitude to alter the frequency of discharge, but the reported suppression is counter to prior reports on the impact of temperature in crayfish nervous tissue.[1] In a second experiment in frogs, ultrasound applied to the spinal cord was able to produce permanent hindlimb paralysis. At lower exposures, reversible paralysis was achievable. In those with permanent paralysis, histological changes, including changes in motor neuron morphology, were observed. Through a systematic study varying parameters such as exposure duration, exposure type (continuous wave or pulsed), and ambient temperature, and comparing to controlled heating via a water bath, the authors demonstrate that thermal effects alone cannot account for the observed tissue effects.



The effect of ultrasound on the frequency of discharge of spontaneously occurring spikes in the excised crayfish ventral nerve cord. Reprinted with permission from W. J. Fry *et al.* Acoust. Soc. Am. 22, 867–876 (1950). Copyright 1950 Acoustical Society of America (Ref. 7).

IMPACT OF THE ARTICLE

Although it is now widely accepted that ultrasound induces bioeffects through both thermal and non-thermal mechanisms, at the time of this study, the field of therapeutic ultrasound was nascent and the mechanisms of action had not been systematically studied. The 1950s and 1960s brought many investigations into the effects of high intensity focused ultrasound in the brain. While there was a strong interest in thermal lesioning with ultrasound, and the Fry brothers[2] and others had successes with these types of exposures in clinical studies, there was also an interest in other effects. It was in studying the effects of pulsed ultrasound exposures that Bakay *et al.*[3] first observed ultrasound-induced modifications to the blood-brain barrier, while the Fry brothers[4] and others such as Ballantine *et al.*[5] were able to report on reversible changes in evoked potentials in mammalian brain exposed to ultrasound. Visionaries in the field, Fry and Fry saw the immense potential of being able to non-invasively, and with high spatial precision, selectively induce effects in the brain. However, it would be over half a century before their pioneering work in thermal and non-thermal effects of ultrasound in nervous tissue would start to reach its potential, as the technology for focusing ultrasound through the human skull bone did not exist until the end of the century, and early studies relied on invasive craniotomies that limited their use. Therefore, although investigators continued to study neurostimulation[6] and other effects of ultrasound in the brain, it was introduction of phased arrays to focus therapeutic ultrasound beams through human skull, first presented in 1998,[7] and the development of noninvasive focusing based on CT derived skull information[8] that reignited broad interest in the field of therapeutic ultrasound use in the brain. Since that time, investigators have been able to build on these early works from Fry and Fry, with the technology ready to bring their interventions to clinic.

CURRENT STATUS

Focused ultrasound use in the brain is now a clinically approved treatment for thermal ablation treating essential[9] and Parkinson's tremor,[10] and has reached clinical investigations for non-thermal effects, such a transient modulation of the blood-brain barrier to enable targeted drug delivery via an cranietomy[11] or through intact skull[12] and neuromodulation.[13] Further, other cavitation based treatments, such as cloth lysis[14] and histotripsy (complete fractionation of soft tissue by short high pressure pulses)[15] are being developed for use in the brain. The Fry brothers took the early experiments of Lynn and coworkers[16,17] and with careful extensive experimental and clinical studies established the various ultrasound interactions with the brain and nervous tissues. Based on this work, they are considered the founding fathers of the field of focused ultrasound, and their legacy is a vibrant research field bringing new, disruptive technologies to the clinical arena.

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