Neuroscientists produce guide for ultrasound use to treat brain disorders in clinical emergencies

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The discovery that low-intensity, pulsed ultrasound can be used to noninvasively stimulate intact brain circuits holds promise for engineering rapid-response medical devices. The team that made that discovery, led by William "Jamie" Tyler, an assistant professor with the Virginia Tech Carilion Research Institute, has now produced an in-depth article detailing this approach, which may one day lead to first-line therapies in combating life-threatening epileptic seizures.

Status epilepticus is a condition in which the brain is in a state of persistent seizure and which, if not halted, can lead to Sudden Unexplained Death in Epilepsy (SUDEP). But, as the recent article by Tyler and colleagues shows, ultrasonic neuromodulation does not necessarily need to be focused to attenuate epileptic seizures, meaning that it can be quickly applied in neurocritical care situations.

"Imagine a device like an automatic external defibrillator except for the brain," said first author Yusuf Tufail, who is now a postdoctoral associate at the Salk Institute for Biological Sciences.

Published in the September issue of *Nature Protocols*, the article, "Ultrasonic Neuromodulation by Brain Stimulation with Transcranial Ultrasound," provides a guide for the further development and clinical application of ultrasonic neuromodulation. The authors — Yusuf Tufail, Anna Yoshihiro, and Monica M. Li of Arizona State University's School of Life Sciences; Sandipan Pati of Barrow Neurological Institute at St. Joseph's Hospital and Medical Center in Phoenix, Ariz.; and corresponding author Tyler — also published their earlier research into the feasibility of this approach in *Neuron* in 2010.

Ultrasound is an acoustic wave occurring at frequencies exceeding the range of human hearing. Uses range from food processing to communication and include medical imaging. Tyler and his research group have spent several years developing noninvasive methods for brain stimulation employing low-intensity, low-frequency (LILFU) ultrasound. "Much of our time had been spent on understanding the biological effects of LILFU on intact brain circuits and how to control neural activity using LILFU," Tyler said.

The team has observed that the mechanical bioeffects of ultrasound are indeed capable of stimulating neuronal activity, meaning that ultrasound could join other therapies for neurological disorders — namely, implanted electrodes, such as those used in deep-brain stimulation, and external magnetic stimulators used for transcranial magnetic stimulation to treat disorders such as Parkinson's disease, major depression, and dystonia. The major advantage of using ultrasound for brain stimulation is that it can confer spatial resolution at millimeter precision while being focused through the skull to deep-brain regions without the need for invasive brain surgery, Tyler said.

"We have also shown that ultrasound can be used to stimulate synaptic transmission between groups of neurons within the brain in a manner similar to conventional implanted stimulating electrodes without generating significant heating of the brain tissue," said Tyler.

"Further studies are required to fully elucidate the many potential mechanisms underlying the ability of ultrasound to stimulate neuronal activity in the intact brain," the article states. However, while using ultrasound for brain stimulation represents a powerful new tool for clinical neuroscience, there are potential concerns, since high-intensity ultrasound is also capable of destroying biological tissues, the researchers write.

The article reports that ultrasound has been used for many hours across many weeks, "stimulating cellular circuits in the living brain without producing damage in mice as assessed with cellular, histological, ultrastructural, and behavioral methods." The researchers added a note of caution: "Additional investigations across animal species and dosage levels are required, however, before the safety can be fully ascertained."

Moving this technology forward will require scientists, engineers, and physicians spanning many disciplines. The impetus for the *Nature Protocols* article is to disseminate basic methods for conducting ultrasonic neuromodulation. "There is a major need for increased open communication among engineers designing ultrasound-based medical devices, neuroscientists studying the core biological effects of ultrasound, and clinicians implementing ultrasound for therapeutic interventions," said Tyler.

The *Nature Protocols* article poses specific questions needing to be addressed, such as how ultrasound affects neurons on a molecular and cellular level, how to correct for impedance mismatches between skin and skull interfaces, and the need for characterizing safety across different exposure times, applications, and disease states.

The research reported in the article provides the provocative demonstration that ultrasonic neuromodulation is capable of attenuating seizure activity during pharmacologically induced status epilepticus in rodents. "While other research groups have reported that focused ultrasound can modulate seizure activity in the brain, the approaches used in those earlier studies require timely preparations and the implementation of MRI to focus the ultrasound in an approach known as magnetic resonance-guided focused ultrasound," said Tyler. "Our findings show that clinicians may not need to take such complicated, costly, and time-consuming approaches to treating patients in critical situations."

More information: www.nature.com/nprot/journal/v … /nprot.2011.371.html

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