

# APPLICATION OF TRANSCRANIAL FOCUSED ULTRASOUND IN NEUROSURGERY

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**Abstract.** Transcranial focused ultrasound is a modern medical technology that allows a noninvasive neurostimulation on the brain. This technique has been developing for about 20 years and a lot of possible applications of the technology are only at the preclinical research stage. The greatest progress has been made in the field of functional neurosurgery when focused ultrasound allows non-invasive therapy to create small destruction areas in the corresponding targets under constant magnetic resonance imaging (MRI) control to have therapeutic neuromodulatory effects upon Parkinson's disease, essential tremor, pain syndromes, obsessive-compulsive disorders and other diseases. To date, this treatment has been provided for more than 300 patients. The single cases of the ultrasonic thermal destruction of intracranial neoplasms have been published recently. The attempts of ultrasonic third ventriculostomy are made to treat animals.

**Keywords:** neurosurgery, technology, noninvasive neurostimulation, transcranial focused ultrasound.

The **aim** of this research is to review the use of focused ultrasound technology in non-invasive neurosurgery. Ultrasound (US) is the propagation of mechanical energy, elastic waves of mechanical vibration in a medium. Ultrasound can be emitted as continuous waves, which are used for thermal destruction, or intermittent pulses, which have neuromodulatory effects.

The **object** of the research is transcranial focused ultrasound.

The **subject** of the research is the application of focused transcranial ultrasound in non-invasive neurosurgery to have therapeutic neuromodulatory effects.

**The research is of topical interest** as it concerns the treatment of neurodiseases in case it is impossible to apply surgical intervention or when patients face personal contraindications to have invasive treatment. In such cases, modern technologies can provide treatment with ultrasound coupled with MRI for various operations without the use of cranial trepanation. Such an innovative form of non-invasive treatment deals with various non-standard neoplasms as well as with complex forms of nervous system diseases with a chance to be cured.

The **methodology** of the research is based on the modern conception of the technique of the Posttransplant Hemolytic Uremic Syndrome (PHUS) that involves the use of one or more sources focusing ultrasound waves with specific parameters at a given point to produce a desired effect there (e.g. destruction, change in vascular permeability) with constant monitoring of a treatment process by means of ultrasound or MRI. Focused ultrasound surgery (FUS) uses waves with a frequency of less than 1 MHz (the frequency of diagnostic ultrasound is 1-15 MHz) that reduces the heating of cranial bones. Tissue thermal destruction is performed with high intensity ultrasound ( $>100 \text{ W/cm}^2$ ) whereas non-thermal exposure is achieved with low-intensity ultrasound.

Experiments on the use of ultrasound for the non-invasive treatment of brain substance were first carried out by J. G. Lynn, R. L. Zwemer, A. J. Chick, A. E. Miller in the early 40s of the 20<sup>th</sup> century and continued by the W. J. Fry et al [1; 2].

In the 1950s, ultrasonic destructions were performed to treat Parkinson's disease and mental disorders. Despite the success, several factors – the need for craniotomy, the impossibility of accurate navigation – limited the wide application of the method. These technical problems were solved only in the late 90s of last century. The problem of exposure through skull bones, which significantly attenuate ultrasound and heat up, was solved with the introduction of multiple synchronized ultrasound systems.

Each source has a controller that determines the phase shift so that waves from different sources reach a target simultaneously. The location of sources on the hemisphere evenly distributes heating on the surface of the skull. Accurate navigation has become possible with the advent of MRI and MRT (magnetic resonance thermometry), which provides non-

invasive interactive temperature monitoring during an ultrasonic thermal destruction procedure.

Mechanical energy in ultrasound is transformed into thermal energy due to the friction of particles in a vibrating medium. After a sufficiently intensive or prolonged exposure, coagulation necrosis develops at 56 °C in 1 sec., at 42 °C in 240 sec.

Ultrasound also causes cavitation. In stable cavitation, microbubbles arising in the tissue or introduced from the outside oscillate, resulting in increase in vascular permeability. Unsteady (collapsing) cavitation involves the expansion and subsequent rapid collapse and rupture of micro-bubbles that is accompanied by the release of significant energy and causes mechanical destruction of tissue. Controlled cavitation-assisted destruction is being investigated, but so far this effect is poorly controlled and is primarily seen as a side effect of thermoablation. The parameters of an ultrasonic wave determine the physical effects, which, depending on the location and conditions of application, can have different biological effects.

Nowadays there are more and more possibilities to carry out examinations with different ultrasonic sources. Naturally, good results require equipment of high quality and precision as well as permeability. All modern clinical studies as well as a significant part of the experimental works are performed on a specialized device. In clinical practice, the device is used for non-invasive ultrasound thermal ablation of intracerebral targets.

The device is currently approved during clinical practice in Europe for thalamotomy for essential tremor and neuropathic pain. It has also been demonstrated in a laboratory to be suitable for disruption by cavitation effects as well as for a local increase in the permeability of the blood-brain barrier.

The modern model of the ExAblate Neuro 4000 (InSightec, Haifa, Israel) is a 30 cm diameter helmet containing 1024 ultrasound sources with a frequency of 650 kHz. The source control system allows for a limited focus of ultrasonic waves in the target. An elastic silicone membrane isolates the space between the sources and the patient's head. Water circulates in this space that prevents the skin and bones of the skull from heating and also acts as a conductor of ultrasound.

The helmet with sources is fixed on a special MRI table which is compatible with General Electric devices having the magnetic field strength of 3 and 1.5 Tesla. It is worth noting that the ExAblate Neuro 4000 and its technology for intracranial targets are currently subject to a number of limitations. In the current model of the device, the zone of possible exposure is limited to an area within about 3.5 cm of the intercommissural line. Exposure to a target outside this zone results in increased bone heating both near the focus and in the vicinity of the cranial vault. A new model has been announced that will have a larger target zone of 6.5 cm in the vicinity of the intercommissural line.

Another issue is the impossibility of achieving the required temperature for thermal destruction in some situations. It is assumed that the limitations can be related to a large volume of the skull above the intercommissural line, the thickness ratio of the compact and cancellous bone of the skull, the shape of the skull and other factors. One way to solve the problem is to introduce microbubbles (ultrasound contrast) into the bloodstream, which can potentiate thermodestruction.

Pre-treatment simulation systems are also being developed that will allow predicting the possibility of thermodestruction even before frame fixation. A feature of the current model is its focus on functional neurosurgery; this results in a small footprint that makes it very difficult to destruct a tumour that can reach a significant size. It has been announced that in a new model of the device the treatment area will be extended to several centimetres.

There are already around 300 patients in the world who benefited from modern technology in the 21st century and there are people whose operations have been carried out using ultrasound. These surgeries must be carried out with the help of sophisticated equipment and highly qualified specialists.

In late 2013 the Rambam Medical Centre in Haifa performed a unique operation using guided ultrasound waves. The operation was performed on the brain under MRI monitoring. Instead of a surgical scalpel, the doctor used ultrasound waves.

A revolutionary breakthrough is that this type of intervention is performed without trepanation of the skull bone and therefore it does not require the use of anesthesia. Since the patient's skull is not opened, there

is no postoperative rehabilitation period and no danger of postoperative inflammation.

The operation was performed in the neurosurgery department of Rambam Medical Center, using ultrasound waves, on a 72-year-old man from northern Israel, who has been suffering from tremor for almost twenty years. The operation lasted about two hours; after the operation the patient managed to get up and walk on his own. Problems with trembling in hand and body disappeared.

The operation was carried out in such a way that a helmet-like device was placed on the patient's head and the helmet emitted high-powered ultrasound waves which were directed strictly at one area of the brain. The localisation was accurate to within a tenth of a millimeter. During the operation, the patient was positioned inside the tomograph while the operating neurosurgeon sat behind the protective screen. The surgeon activated the helmet device which started emitting ultrasound waves.

The joystick allows the waves to be accurately directed to the area to be burned out that is detected by the real-time MRI scans. The patient was not put under anaesthesia and was fully conscious. During the operation, the neurologist constantly asked questions and monitored the patient's condition, checking his reflexes and ability to function. Just ten minutes after the operation began, one could see a significant improvement in cognitive function: The patient began to control the movements of his own hands.

The surgeries have taken place in America, South Korea, Sweden and Israel. For the first time, doctors have shown that it is possible to successfully perform the most complex brain surgeries without complications accompanying such operations. Other effects are just being introduced into practice.

For example, there are reports of the use of the technique in cancer (thermal destruction of tumours, increase in the permeability of the GEB for chemotherapy). Some techniques have not yet gone beyond research laboratories (cavitation-assisted intracranial target destruction, non-destructive neuromodulation). Some applications of FUS are at an early stage of development and are only potentially being considered for the treatment of CNS pathology. For example, sonodynamic therapy like photodynamic therapy is being considered.

To summarise, ultrasound technique is very promising nowadays and can be developed and refined. Depending on its parameters, PHUS produces several different biological effects that can be used for diagnostic or therapeutic purposes. Some applications of the technology (thermal destruction of targets in the treatment of Parkinson's disease, essential tremor, etc.) are already used in therapeutic practice in clinics in some countries.

They have been adopted as a treatment option. Significant technical, research and clinical work remains to be done on the way to establishing the technique. Nevertheless, it is already possible to state the emergence of a new clinical tool that will complement the existing surgical and radiotherapy methods for the treatment of CNS diseases.

### **Reference**

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