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Focused Ultrasound as a Tool to Input Sensory Information to Humans (Review)

L. R. Gavrilov[a] and E. M. Tsirulnikov[b]

[a] *Andreev Acoustics Institute, Russian Academy of Sciences, ul. Shvernika 4, Moscow, 117036 Russia*
e-mail: gavrilov@akin.ru

[b] *Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, pr. M. Toreza 44, St. Petersburg, 194223 Russia*
e-mail: tsiruln@iephb.ru

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Abstract—This review is devoted to the analysis of studies and implementations related to the use of focused ultrasound for functional effects on neuroreceptor structures. Special attention was paid to the stimulation of neuroreceptor structures in order to input sensory information to humans. This branch of medical and physiological acoustics appeared in Russia in the early 1970s and was being efficiently developed up to the late 1980s. Then, due to lack of financial support, only individual researchers remained at this field and, as a result, we have no full- fledged theoretical research and practical implementations in this area yet. Many promising possibilities of using functional effects of focused ultrasound in medicine and physiology have remained unimplemented for a long time. However, new interesting ideas and approaches have appeared in recent years. Very recently, very questionable projects have been reported related to the use of ultrasound for targeted functional effects on the human brain performed in some laboratories. In this review, the stages of the development of scientific research devoted to the functional effects of focused ultrasound are described. By activating the neuroreceptor structures of the skin by means pulses of focused ultrasound, one can cause all the sensations perceived by human beings through the skin in everyday life, such as tactile sensations, thermal (heat and cold), tickling, itching, and various types of pain. Stimulation of the ear labyrinth of humans with normal hearing using amplitude-modulated ultrasound causes auditory sensations corresponding to an audio modulating signal (pure tones, music, speech, etc.). Activation of neuroreceptor structures by means of focused ultrasound is used for the diagnosis of various neurological and skin diseases, as well as hearing disorders. It has been shown that the activation is related to the mechanical action of ultrasound, for example, by the radiation force, as well as to the direct action of ultrasonic vibrations on nerve fibers. The action of the radiation force is promising for the realization of the possibility of blind and even deaf-and-blind people to perceive text information on a display using tactile sensations caused by ultrasound. Very different methods of using ultrasound for local stimulation of neuroreceptor structures are discussed in this review. Among them are practical methods that have been already tested in a clinic, as well as pretending to be sensational methods that are hardly feasible in the foreseeable future.

Keywords: focused ultrasound, sensory information, neuroreceptor structures, sensations, stimulation, radiation force, medicine, physiology.

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INTRODUCTION

Searching for artificial stimuli that can induce sensations noninvasively and locally has always been an important task of physiology and medicine. Such stimuli would be extremely useful in medicine, for example, in diagnosis of diseases associated with changes in various sensations, as well as in physiological studies. It is necessary to exclude any damage to the site affected by the stimulus or surrounding tissues, as well as to provide prolonged and repeated use of such artificial stimuli. It is important to perform accurate measurements of various parameters of stimuli.

Electric current has always played an important role as an artificial stimulus of neural structures. However, it is often impossible to use electric current for local stimulation of individual receptor or neural structures without affecting the neighboring area. In the case in which it is necessary to affect deep structures, surgery is needed to bring electrodes to them, which contradicts to the important biological requirement of noninvasive functional impact.

As shown below, the method of activating neuroreceptor structures with focused ultrasound entirely satisfies the requirements of contactless, noninvasive, local, and dosed effects. Functional effects arising from the use of ultrasound are extremely diverse. They range from temporary reversible supression of functions to the appearance of a propagating excitation. The review is focused on the stimulating (i.e., activating or irritating) effect of focused ultrasound on the neuroreceptor structures that can be repeated many times (sometimes, for years) without any risk of damaging the structures and surrounding tissues.

REVERSIBLE EFFECTS AT THE ACTION OF ULTRASOUND

Functional (reversible) effects of the action of ultrasound on neuroreceptor structures have been well known since the middle of the last century, i.e., two decades before the research the authors of this review had been started. Interest in the possibility of reversible inhibition of the functional activity of some brain structures using ultrasound was aroused by a number of practical tasks in medicine. For example, it could provide high accuracy in irradiation brain structures by powerful focused ultrasound during ultrasonic neurosurgical operations by means of a preliminary action of deliberately nondestructive ultrasonic doses that could result in reversible changes in these structures. This would simplify complicated and time-consuming methods based on the finding of intracranial and cerebral marks. According to Lele [1], the problem of obtaining reversible changes in brain structures is crucial for implementation of focused ultrasound in clinical neurosurgery. Using ultrasound would also be extremely useful for studying the functions of different parts of the brain and structural and functional relationships in the central nervous system.

W. Fry et al. were among the first researchers to study the effect of ultrasound on the conduction of nerve fibers [2]. The action of ultrasound with an intensity of 35 W/cm^2 (frequency of 0.98 MHz) on the conductivity of the ventral nerve cord of the lobster caused the effect of reversible inhibition. The frequency of spike potentials first increased and then decreased, and within about 40 s after the action, large potentials completely disappeared. Twenty-five seconds after turning off the ultrasound, they reappeared and gradually increased. Then, 40 s after turning off the ultrasound, they reached the initial amplitude and frequency.

These studies were further developed in the same laboratory [3–6]. In particular, it was shown [4] that the effect of focused ultrasound of relatively high-intensity on the lateral geniculate nucleus of a cat's brain causes reversible inhibition of electrical responses in the visual cortex to light stimulation of the eyes. Complete restoration of visual function occurred within 30 min after the irradiation. No morphological changes in the irradiated nerve tissue were observed.

The reversible effect of the focused ultrasound with a frequency of 2.7 MHz on the Edinger–Westphal nucleus, the activity of which is related to the regulation of dilation and contraction of the pupil, was studied in the experiments on cats [7]. Destruction or stimulation of these nuclei leads to a distinct pupillary reaction. Irradiation was performed by a sequence of pulses with an intensity at the focus of 1700 W/cm^2, duration of 0.14 s, and frequency of ones 1/3 Hz; the number of pulses ranged from 1 to 13. It was found that, in several experiments, pupillary dilation and contraction were not accompanied by histological changes in the irradiated tissue.

P.P. Lele [8] studied the effect of focused ultrasound with a frequency of 0.6–2.7 MHz on the conductivity of the peripheral nerves in cats, monkeys, and humans. It was found that the ultrasonic dose required for blocking the conductivity of the nerve decreased with an increase in the environmental temperature in the irradiated region. According to Lele, all physiological effects associated with the effect of ultrasound on the nerve fibers can be reproduced using dosed application of heat to certain regions of the nerves. That is, Lele suggests that the effect that ultrasound has on the conductivity of nerve fibers has a thermal nature.

When affecting the sciatic frog nerve by focused ultrasound in a number of particular modes, the thin nerve fibers can be blocked without changing the conductivity of the thick fibers [9, 10]. The peculiarity of this method was that the nerve was placed into a rubber block. As a result, the temperature of the nerve increased significantly more compared to the effect of ultrasound *in vivo*, as the absorption coefficient of ultrasound in rubber is very high.

According to P.O. Makarov et al. [11–13], when applied to a nerve trunk, ultrasound does not cause the spreading of excitation in the nerve or in individual nerve fibers, although it changes some of their functional properties. At the moment, the possibility of activation of free nerve endings, single A–delta nerve fibers, and C–fibers using focused ultrasound has been proven experimentally [14–25]; however, neither local impulse activity nor propagating excitation have been achieved by means of direct action of ultrasound on brain structures.

Theoretical study by W.J. Fry [26] is interesting from this point of view. In this study, a method of electrical stimulation of the neural tissue in the deep structures of the brain without placing electrodes inside the brain is suggested. The essence of the method is based on the interaction of an alternating electric field applied to the brain from outside and the acoustic field generated by focused ultrasound localized in the site of stimulation. In the simplest case, the electric and acoustic fields have the same frequency. Spreading of the acoustic oscillations in tissue is accompanied by temperature changes. Since the electrical conductivity of the tissue depends on the temperature, the acoustic field causes periodic changes in these parameters with maximal variations in the focal region. Tissues expand when heated, and contract when cooled. As a result, the electric current that flows in the tissue during the half-period when the pressure increases does not have the same value as the current that flows in the opposite direction during the negative half-period. Thus, "rectification" a small part of an alternating electric current, i.e., an unidirectional transfer of the charge takes place. Its magnitude depends on such factors as the parameters of acoustic and electric fields, electrical conductivity of the tissue, and frequency-dependent absorption coefficient of the tissue. However, calculations show that stimulation of nerve cells using this method requires powerful acoustic and electric fields, the prolonged effect of which may lead to destruction of the nerve tissue.

V.A. Zuckerman suggested an interesting idea regarding the possibility of stimulation of brain neurons not only by the local action of convergent ultrasound waves, but by weak shock waves as well [27].

Studies of the reversible changes in the brain structures of animals under the effect of focused ultrasound were initiated by the Institute for Brain Research of the Soviet Academy of Medical Sciences together with the Acoustics Institute in the late 1970s. The study was developed in two directions. The first direction was related to reversible shutdown of the visual function under the effect of focused ultrasound in animals [28–30]. The changes in the evoked potentials recorded in the visual tract and visual cortex under the action of light stimulation of eyes were studied in cats. Focused ultrasound with a frequency of one megahertz in the pulsed mode was used. The intensity of the ultrasound pulse ranged from 7 to 63 W/cm^2, the duration was 5–50 ms, the pulse–repetition frequency was 0.5–50 Hz, and the total exposure time was 10–60 s. The nature and duration of the changes in the evoked potentials were determined by the parameters of the effect and varied widely in the dependence of these parameters. In some cases, suppression of the evoked potentials was full; in other cases, it was partial. The changes of the potentials were reversible, partially reversible, or irreversible. Fully reversible suppression of the evoked potentials in the visual tract followed by full restoration of their shape and amplitude appeared to be the most interesting for application. The suppression lasted from a few seconds to tens of minutes. The effect was achieved with nondestructive ultrasonic dosages, which made it possible to affect the structure repeatedly without risk of damage. The temperature increase did not exceed fractions of a degree, which excluded heat from the main factors affecting the visual tract. An experiment [28] is important from the methodological point of view. In this experiment, a unit with a built-in relatively small (diameter 18 mm) focusing transducer was fixed on the head of an animal in such a way that the focal region of the transducer was aligned with a targeted exposure site. During suppression of the evoked potentials, the animal was not immobilized or anaesthetized. Its brain structures were exposed to focused ultrasound in the course of animal's behavioral act.

The second branch of research was related to the study of the shifts of the constant potential in various brain structures of rats (in the cerebral cortex, hippocampus, optic thalamus, and caudate nucleus) under the action of ultrasound on these structures [31, 32]. The impact of focused ultrasound was realized with a frequency of 4.6 MHz and intensity of 5–100 W/cm^2 in pulsed mode, with pulse repetition frequency of 5–200 Hz, pulse duration of 10–100 ms, and exposure time of 10–40 s. Special attention was paid to the study of the spreading depression that occurs in the brain in response to many types of stimuli, in particular, to ones induced by focused ultrasound.

We should mention study [33] that includes acute experiments on cats and chronic experiments on rabbits, in which irradiation of different cortical fields with focused ultrasound was performed in the intact skull or after craniotomy. Long-term (up to 20 min) impact of focused ultrasound with intensities of 1–10 mW/cm^2 resulted in increased excitability of the cortex to the action of other stimuli, such as light and electrical current, which was reflected in an increase in the amplitude of potentials evoked by light stimuli, and a decrease in the threshold of a response to direct electrical stimulation of the cortex. Affecting the cortex by single ultrasound pulses from 0.1 to 100 ms, and pulse series of 1–20 pulses/s at the calculated intensities from 1 μW/cm^2 to 1400 W/cm^2 in the focal region did not lead to evoked potentials.

Some functional effects of ultrasound on sensory and motor structures in the brain of animals were discovered in studies conducted at the Sechenov Institute of Evolutionary Physiology and Biochemistry of the Soviet Academy of Sciences together with the Acoustics Institute [20]. The ultrasound frequency was 2.34 MHz. The irradiation was performed in continuous (up to 30 s) and pulsed modes (pulse duration of 1 and 10 ms, repetition rate from 0.5 to 50 Hz). The intensity averaged over the area of the focal region varied from 3 to 580 W/cm^2. The number of pulses with each intensity ranged from 1 to 50, the duration of series did not exceed 1 s. Various brain structures of the grass frog served as targets. At irregular time intervals after exposure to ultrasound, microphone potentials in the inner ear, potentials of the auditory center of the midbrain caused by sound, displacement of the eyeball, changes in the diameter of a pupil, the slope of the head and trunk in stationary frogs, the direction of motion while jumping, and changes in the pattern of the vocal reaction were estimated. Morphological control of the irradiated area was carried out. The suppression of microphonic response to sound, a decrease in the amplitude of the potentials in the midbrain caused by the sound, the displacement of the eyeball from its normal position, long-term dilation or contraction of the pupil and changes in its reaction to light, movement of the animal in a circle with an inclined head, and changes in the temporal pattern of its vocal reaction were observed. The degree of manifestation and reversibility of the above reactions depended on the parameters of ultrasound exposure and, primarily, on the mode of irradiation. In a pulsed mode, compared with a continuous mode, of irradiation, the reactions were more pronounced and more complete and the recovery time was smaller. It was found that, despite the clear changes in functional performance, there were no morphological changes in brain tissues during irradiation in a pulsed mode.

We summarize the results of this section.

(1) Although the possibility of changing the functional state by focused ultrasound has been experimentally proved, spreading excitation in the form of spike activity under direct action of focused ultrasound on central neural structures has not been obtained.

(2) As a rule, functional effects recorded are expressed in the form of suppression or reduction of functional activity, but not in the form of its initiation or increase.

(3) The ultrasonic doses required for obtaining the above effects usually are comparable to the threshold destructive doses. From this arises the question of the safety using such effects. This fact is probably one of the reasons that the described above effects have not yet been put into practice in physiology and medicine.

As already mentioned, not those ultrasonic stimuli that cause only local single effects, but stimuli that cause long–term and repeated actions without the risk of injury for tissue and nerve structures, are promising in medicine and physiology. Further discussion is devoted to studies on using this kind of ultrasonic stimuli.

APPLICATION OF FOCUSED ULTRASOUND FOR STIMULATION OF NEURORECEPTOR STRUCTURES (STUDIES IN THE 1970–80s)

Studying the possibilities of stimulation of neuroreceptor structures with focused ultrasound pulses started at the early 1970s by the Acoustics Institute together with a laboratory of the Sechenov Institute of Evolutionary Physiology and Biochemistry, headed by the famous Russian physiologist and Corresponding Member of the Soviet Academy of Sciences G.V. Gershuni (1905–1992). Almost immediately this research was joined by a laboratory of the I.P. Pavlov Institute of Physiology headed by Doctor of Biological Sciences O.B. Il'inskii. As proposed by Gershuni, the human hand was the initial object of study. The skin and tissues of the hand contain a large number of neuroreceptor structures. Mechanical, thermal, and other irritants serve as adequate stimuli for them. Obviously, these studies, especially in their early stages, were much safer than studies on the structures of the central nervous system. In addition, the objects of study included Pacinian corpuscles, single mechanoreceptors, isolated from the cat intestinal mesentery, as well as frog ear labyrinth.

An experimental set-up used for the research on the human hand is shown in Fig. 1 [34]. Ultrasonic frequency varied widely; however, in most experiments, the focusing transducers with frequencies of 0.48, 0.87, 1.95, and 2.67 MHz were used [34–37]. A focusing transducer and the hand of a subject were placed in the test bath with settled or distilled water, and the hand was fixed in a special casting (Fig. 1). A removable pointer of the focus mounted on an ultrasonic transducer allowed the researchers to control the position of the center of the projection of the focal region. In most cases, the diameter of the radiating element of the focusing transducer was 85 mm, the radius of curvature was 70 mm, and the convergence angle of the transducer was 36°. As is well known, the form of the focal region is an ellipsoid of revolution. The diameters of the focal region for the frequencies 0.48 and 2.67 MHz and the chosen geometry of the radiating element were 6.4 and 1.1 mm, and the areas were 32 and 0.95 mm^2, respectively.

As usual, neuroreceptor structures were stimulated by single pulses of specified durations (e.g., from 100 μs to 100 ms and, as an exception, up to 500 ms) with an intensity in the focal region from a few W/cm^2 to thousands of W/cm^2 (for the shortest pulses). In some experiments, especially when studying pain, series of pulses with different repetition rates were used. Randomly selected points on the skin of fingers, palms, and forearms were affected by focused ultrasound. On the bases of the reports of subjects after the action of ultrasonic stimuli, the absence or presence of sensations and descriptions of subjective characteristics were recorded and the thresholds of sensations were measured. Other methodological peculiarities of the investigation of the stimulatory effect of focused ultrasound have been described in books written by authors of this review or with their participation [20, 34, 36].

The possibility of activating neuroreceptor structures in humans using short (with a duration on the order of units or fractions of milliseconds) pulses of focused ultrasound was first shown [34–37]. It was found that focused ultrasound on the skin can cause all the sensations that people routinely receive through the skin, such as tactile, thermal (heat and cold), tickling, and itching, as well as various types of pain, including deep-seated pain in muscles, periosteum, etc. [34–37]. The thresholds of different sensations were usually measured in the units of intensity of ultrasound, and, for subjects with normal sensitivity, they were well reproducible. The variation of measured values did not exceed the data scattering in standard psychophysical experiments. If necessary, the values of threshold intensity were converted into values of other parameters of focused ultrasound through well-known relations for a plane wave, bearing in mind that the plane wave passes through the focal plane [38, 39].

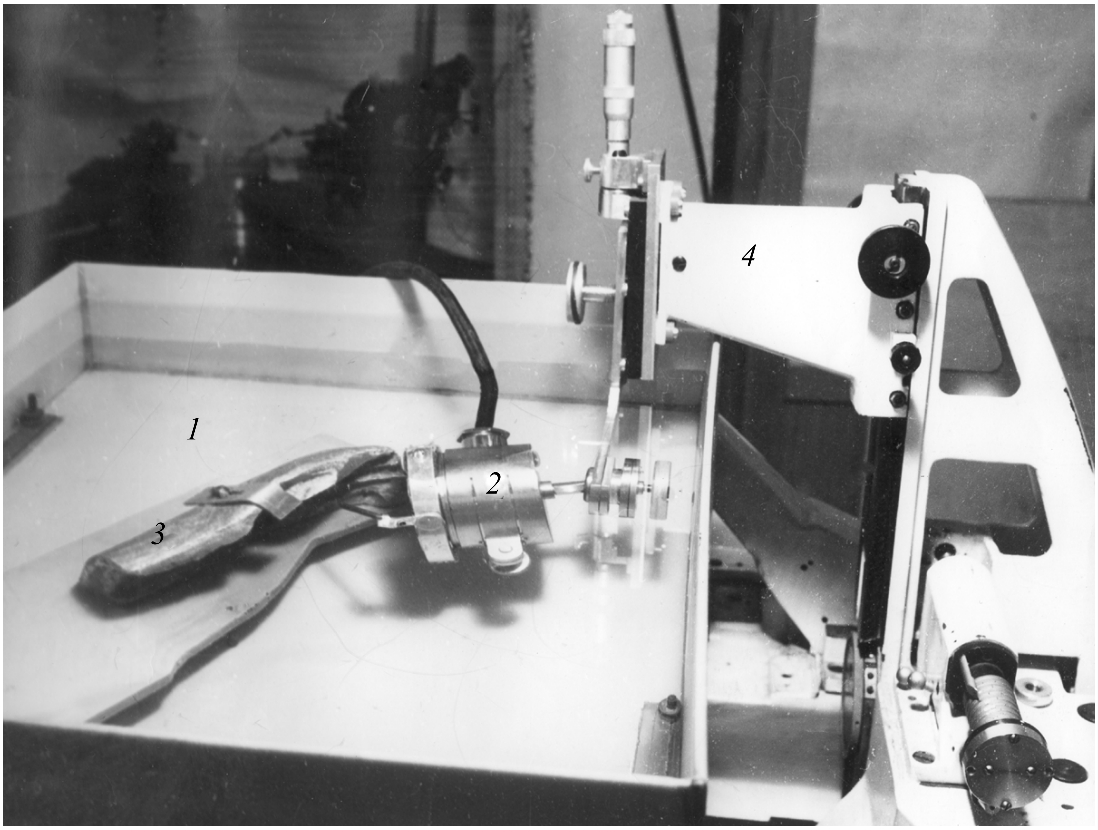

Fig. 1. Apparatus for investigation of somatosensory sensitivity in human beings: *1* water bath, *2* focusing ultrasound radiator, *3* the casting to fix the arm of a subject, and *4* coordinate device.

Table 1 [34] presents the order of magnitude of the thresholds of tactile, thermal, and pain sensations on the skin of fingers effected by stimuli with a duration of 1 ms and different ultrasonic frequencies.

The thresholds of parameters given for a single experiment do not depict general results. In particular, they decreased with an increase in the duration of exposure and significantly depended on the location of the effected region on the skin [24, 40, 41]. In some experiments, especially when studying the thresholds of pain, series of pulses with a selected duration were used [34].

This research allowed the hypothesis that the same neural structures of the skin are related to the sensations of heat and cold to be proved. The appearance of this or that sensation depends, ultimately, on the relationship of the internal body temperature and the ambient temperature [42–44].

Parameters of stimuli of focused ultrasound with a duration of 1 ms corresponding to the appearance of threshold sensations of different modalities at different ultrasonic frequencies

Sensations	Tactile				Heat				Pain			
frequency, MHz / parameters	0.48	0.887	1.95	2.67	0.48	0.887	1.95	2.67	0.48	0.887	1.95	2.67
Intensity I, W/cm^2	8	15	80	120	55	90	1420	3200	55	140	2860	–
Displacement amplitude A, μm	0.1	0.08	0.08	0.08	0.28	0.20	0.35	0.40	0.28	0.24	0.50	–
Sound pressure P, atm	4.9	6.7	15.5	19	13	16.5	65	98	13	21	93	–
Oscillation velocity V, m/s	0.3	0.45	1.0	1.35	0.85	1.1	4.3	6.7	0.85	1.35	6.1	–
Increment of temperature ΔT, °C	0.0002	0.006	0.01	0.02	0.001	0.004	0.14	0.41	0.001	0.006	0.27	
Acoustic power W, W	2.56	1.35	1.4	1.14	17.6	8.1	25	30.4	17.6	12.6	50	–

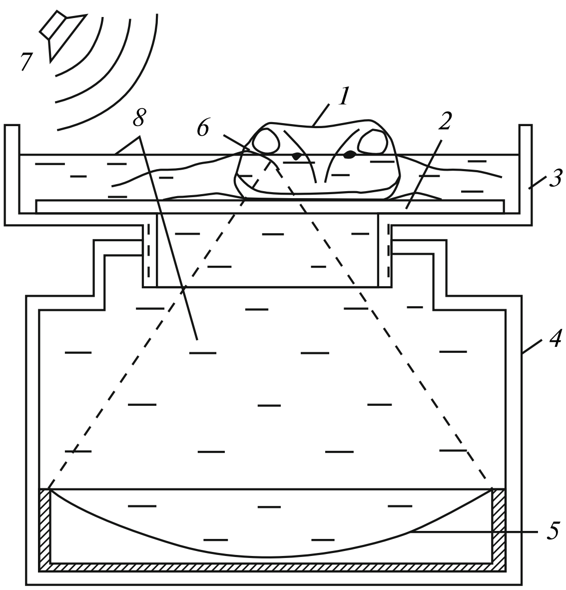

Fig. 2. Scheme of apparatus for affecting the ear labyrinth of an animal by focused ultrasound: *1* experimental animal, *2* stand fixing the animal, *3* pan, *4* housing for mounting the pan and focusing radiator, *5* focusing radiator, *6* center of the focal region, *7* loudspeaker, and *8* water.

The advantages of the proposed method of stimulating neuroreceptor structures using focused ultrasound are

(1) the method is noninvasive, since it does not need surgery to access the deep structures;

(2) the size of a stimulated region can be controlled and varied by changes in ultrasonic frequencies and the parameters of a transducer, which provides selectivity and locality of the effect on neuroreceptor structures;

(3) it is possible to control accurately the parameters of the ultrasonic stimulus, such as intensity, duration, volume, area of influence, and repetition frequency of stimuli; and

(4) it is possible to affect not only the skin, but also tissues located deep in the body.

The grounds and implementation of ultrasonic method for introduction auditory information to humans became a separate branch of research. Studies in this field began in the mid–1970s and were performed jointly by the Sechenov Institute of Evolutionary Physiology and Biochemistry; the Leningrad Institute of Ear, Nose, Throat, and Speech; and the Acoustics Institute. Preliminary studies were carried out on the grass frog [45, 46]. The experimental set is shown in Fig. 2 [46]. The ultrasonic frequency was 480 kHz; single stimuli with durations of 0.1–100 ms were used. When the frog ear labyrinth was stimulated by pulses of focused ultrasound, potentials similar to responses to sound stimuli were recorded in the auditory region of the midbrain. Under the joint action of sonic and ultrasonic stimuli, interaction between the responses to them was observed. The thresholds of the appearance of responses to ultrasonic stimulation depended on the duration of stimuli. For example, when the ultrasound frequency was 0.5 MHz, for the duration of a stimulus of 0.1 ms, the threshold intensity was about 1 W/cm^2, and, for the duration of 100 ms, it was 0.01 W/cm^2. Thus, using the ultrasound with these intensities excluded the destruction of tissues, however, it caused the observed responses.

In a more recent study related to the subject under discussion, similar experiments were carried out on cats [47]. A flat ultrasonic transducer with a diameter of 0.6 cm, ultrasonic frequency of 5 MHz, and intensity of 0.3 W/cm^2 was used. The duration of a pulse was 10–70 μs. The transducer was placed over the dura mater of an animal. Auditory sensations that appeared in the animal were monitored by measuring evoked potentials. The authors attributed these sensations to the action of the sound waves, resulted from radiation pressure, propagating through the skull to the auditory organ.

The data on the safety of ultrasonic stimulation of the auditory organ obtained in animal experiments served as a basis for similar studies on humans, as a result of which a method of ultrasonic input of hearing information was proposed [14, 20, 34, 48]. The essence of the proposed method is that the ear labyrinth is affected by focused amplitude-modulated ultrasound. The carrier frequency is significantly higher than the upper threshold of human hearing frequencies (for example, within 0.5–5 MHz), and modulating frequencies correspond to the transmitted acoustic information. Since the ear labyrinth is affected by amplitude-modulated ultrasound, the human is subjected to the oscillations with frequencies of f and $f \pm F$, where f and F, respectively, are the carrier frequency and the envelope, i.e., oscillation in the megahertz frequency range that are inaudible to humans. It was shown that with the propagation of amplitude–modulated ultrasonic oscillations in a heterogeneous medium, demodulation of ultrasonic signal occurs corresponding to auditory information transmitted. Since the amplitude of the low-frequency signal increases with an increase in ultrasonic intensity, the sound pressure of the informative low-frequency signal is maximal in the focal plane of the transducer; with substantial defocusing of an ultrasonic beam, it is maximal in the place of the maximum intensity of ultrasound. Thus, using the proposed method, auditory information can be inputted into the human ear labyrinth, avoiding the usual natural way of the sound waves to the ear labyrinth.

In experiments with persons with normal hearing, testing of the proposed method of input auditory information into the ear labyrinth was performed [48]. Part of the experimental setup is shown in Fig. 3 [49]; a patient and a focusing transducer placed in distilled water-filled sound transparent bag are shown in the photo. The patient laid on a bench and stayed in a horizontal position during the experiments. The water in the bag was heated to a temperature comfortable for the patient.

Matching the focal region with a chosen exposure region was carried out using a coordinate system [20, 34], part of which is shown in Fig. 3. The limits of controlled movement of a transducer relative to the object were the following: 100 mm in a horizontal plane, 1000 mm in a vertical plane (coarse adjustment), and 50 mm in a vertical plane (fine adjustment). The error of determination of the coordinates for each of three mutually perpendicular directions was no more than 0.1 mm. A bag with a focusing transducer was tightly contacted with the head of the subject in such a way that there was no air gap. To improve the quality of the acoustic contact between the radiator and the target, the surface of the bag was smeared with a thin layer of petroleum jelly or special gel. A focusing transducer was equipped with a removable focus pointer, the tip of which coincided with the center of the focal region. The tip of a focus pointer was aligned with a point on the surface of the subject, conventionally accepted as the coordinate origin. Then a focus pointer was removed, and a transducer was moved in three mutually perpendicular directions so that the focal region of the transducer coincided with a presumed site of impact which was the ear labyrinth.

The frequency of focused ultrasound ranged from 0.67 to 3.7 MHz. Ultrasonic generator provided the performance in a pulsed mode, as well as in the modes of amplitude-modulated oscillations and pulse–amplitude modulation. When performing in a pulsed mode, the duration of ultrasound stimulus was adjustable from 0.1 to 1 ms at a repetition rate from 5 to 1000 Hz. In the mode of amplitude-modulated oscillations, the modulation frequency ranged from 20 to 20000 Hz, the modulation coefficient ranged from 0 to 1. In addition, the signals from the microphone, tape recorder, and radio were used as the modulating signals.

In the case of affecting the ear labyrinth with focused ultrasound in a continuous mode of irradiation without any modulation in amplitude, all subjects lacked auditory sensations when increasing the intensity of ultrasound in the focal region up to 120 W/cm^2 (the intensity was not increased more for safety reasons). In the pulse mode, the subjects heard slightly distorted tones, the pitch of which corresponded to a pulse repetition frequency. For a control comparison, the pure tones supplied by the sound generator the headphone were used. The threshold auditory sensations were observed in subjects at an intensity of ultrasound in the focal plane of the transducer of about 0.1 W/cm^2 and at a frequency of 0.67 MHz. The threshold intensities of ultrasound at the focal region, corresponding to the emergence of auditory sensations in humans, discussed here and below are given without taking into account the attenuation of ultrasonic energy in bones and soft biological tissues on the path

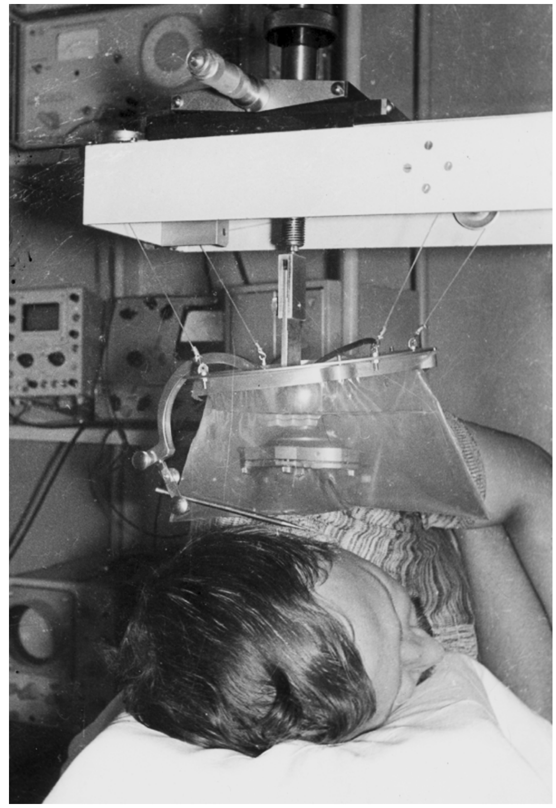

Fig. 3. Apparatus for studying auditory sensations caused by amplitude-modulated focused ultrasound.

of the converging ultrasonic beam to the ear labyrinth, which is difficult to measure. Thus, the real values of the threshold intensities in the tissues are significantly less than those discussed.

When using focused ultrasound modulated in amplitude by sinusoidal oscillations with frequencies ranging from 50 to 15000 Hz, the subjects experienced auditory sensations of tones the pitch of which corresponded to the frequency of modulating signals. The volume of the audible tones increased with the modulation coefficient. By varying the frequency of the sinusoidal modulating potential at a fixed modulation coefficient and recording the intensities of ultrasound corresponding to the appearance of threshold auditory sensations, one could draw frequency-threshold curves as is customary in audiometric studies. The frequency-threshold curves for a subject with normal hearing are shown in Fig. 4. The vertical axis represents the thresholds of ultrasound intensity averaged over the period of modulating oscillations. The horizontal axis represents the frequency of modulation. The parameter is the coefficient of modulation. The carrier frequency was approximately 1 MHz. It is evident that the nature of relationships, especially at modulation frequencies of 1–2 kHz, is similar to the type of curves of the thresholds of perception of sound signals by human beings [50]. It is also evident from

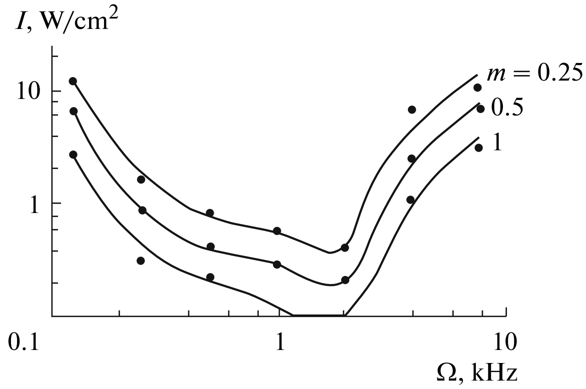

Fig. 4. Typical dependences of threshold intensities of ultrasound in the focal region corresponding to the emergence of auditory sensations from the modulation frequency and modulation coefficient m.

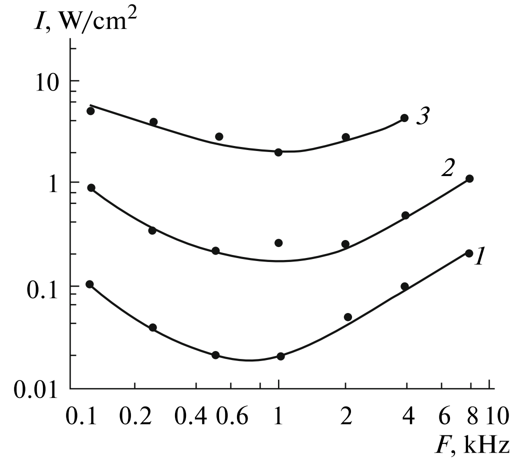

Fig. 5. Frequency-threshold curves for one subject with a modulation coefficient $m = 1$ and different ultrasonic frequencies, MHz: curve *1* for $f = 0.67$, curve *2* for $f = 2.47$, and curve *3* for $f = 3.7$ MHz.

the graph that, for each fixed modulation frequency, auditory sensations appear when the product of the coefficient of modulation m on intensity exceeds a certain constant value.

The dependence of the threshold intensity of ultrasound from the carrier frequency when it changes from 0.67 to 3.7 MHz is shown in Fig. 5. In all cases, the value of the modulation coefficient is 1. It is evident that an increase in the carrier frequency leads to a significant increase in the value of the threshold intensity.

When using focused ultrasound modulated in amplitude by oscillations of complicated form, for example, signals from a microphone or tape recorder, the subjects heard the transmitted auditory information (speech, music) and evaluated its acoustic quality as rather high.

Let us draw some general conclusions regarding to all the methods of using focused ultrasound for input of information through various sensory channels presented in this section. If an impact on a region with the possible minimum area is not a goal of the study, the use of possibly low ultrasonic frequencies is appropriate. This reduces the threshold intensities required for the activation of neural structures, as well as minimizes the losses due to ultrasound attenuation in tissues, particularly when affecting deep structures. In cases in which the power of a generator is insufficient for activation of neural structures using a single stimulus of a given duration, it is reasonable to use a series of pulses of less fixed intensity and record the number of pulses necessary to achieve the needed effect.

It is interesting to compare these results with data on the auditory perception of ultrasound studied in detail by B.M. Sagalovich et al. [51, 52]. It is well-known that human beings can hear sounds with frequencies much higher than 16–20 kHz (the normal limit for hearing in the air) if the radiator is in direct contact with the tissues of the body. This results in the sensation of a high-pitched tone. The pitch does not change when the ultrasonic frequency increases up to 225 kHz (the highest frequency at which these sensations have been registered). The radiator can be applied to various sites of the head, neck, and torso, which results only in changes in the strength of sensations, but not in their tone. In contrast with this method, the impact on the ear labyrinth of humans using amplitude-modulated focused ultrasound allowed the experimenters to input complicated auditory information (speech, music, etc.) with high-quality hearing.

The results of studies on human beings and animals suggest that ultrasound is a universal stimulus for neuroreceptor structures. For example, the effect of focused ultrasound on the human tongue causes peculiar taste sensations similar to ones during stimulation of the tongue with weak electric current. Experiments on Black Sea skates showed that stimulation of electroreceptors by focused ultrasound increases the spike activity in afferent nerve fibers [53]. Studies on invertebrates have showed the ability of focused ultrasound to activate not only receptor structures, but also central nervous structures [54]. However, it is important to note that, in studies on vertebrates (frog, rat, rabbit, and cat), functional activation of brain structures using focused ultrasound was not achieved. There is also no evidence of the initiation of visual sensations due to the effect of ultrasound on the retina of animals [55].

MECHANISMS OF STIMULATING EFFECTS OF ULTRASOUND

Obviously, understanding the mechanisms of stimulating (activating, irritating) action of focused ultrasound on the structures responsible for skin and tissue sensitivity, as well as the emergence of auditory and other sensations, is necessary for the efficient and safe use of ultrasound as a mean of inputting sensory information to human beings. Therefore, studying these mechanisms has always evoked special interest [34, 49, 56, 57].

Let us run through the mechanism of auditory sensations under the effect of amplitude–modulated focused ultrasound on the human ear labyrinth. The ear labyrinth is an extremely sensitive organ, aimed to perceive even very weak mechanical oscillations. It is therefore necessary to take into account the effect of the sound that arises due to radiation pressure produced by amplitude-modulated ultrasound on the ear labyrinth. It is well known that the radiation pressure S is related to the oscillation amplitude A as $S = 1/2\rho\omega^2 A^2$, where ρ is the density of the medium, and ω is angular frequency. If a high-frequency ultrasonic signal with a frequency f is modulated by a low-frequency audio signal according to the law $a\cos\Omega t$, where $\Omega = 2\pi F$ (F is the modulation frequency), the amplitude A should be replaced with the value $A + a\cos\Omega t$. Then [58]

$$S = (1/2)\rho\omega^2 (A + a\cos\Omega t)^2 = (1/2)\rho\omega^2 A^2 \times \left(1 + m^2/2 + 2m\cos\Omega t + (1/2)m^2\cos 2\Omega t\right), \quad (1)$$

where $m = a/A$ is a coefficient of modulation.

It follows from (1) that an amplitude-modulated ultrasonic signal, in addition to the constant radiation pressure, contains a variable radiation pressure with a frequency of $P_F = 2m\cos\Omega t$ and its second harmonic $P_{2F} = (1/2)m^2\cos 2\Omega t$. Thus, if the receptor apparatus in the human ear labyrinth functions normally, the effect of sound oscillations that arise due to the variable component of radiation pressure is one of the most probable causes of auditory sensations. In this case, adequate sound information is delivered to the ear labyrinth, and ultrasound is the only means of delivering this information in the labyrinth. However, as will be shown below, the mechanism of action of ultrasound is not only delivering the sound information, but also providing direct stimulation of the neuroreceptor structures of the ear labyrinth as well.

The mechanisms responsible for the emergence of tactile and thermal sensations, such as heat or cold, are more complicated. The presence of sensations of cold produced by focused ultrasound stimulation allowed to assume that the nature of sensations resulting from ultrasonic stimulation of neuroreceptor structures is not always related to the action of adequate stimuli (for example, the action of mechanical stimulus on the mechanoreceptors or a heat stimulus that causes the sensations of heat), as ultrasound obviously does not carry cold in itself. The above-mentioned data on taste sensations and reactions in the nerve fibers of skates obtained using focused ultrasound [53] also lead to the conclusion that activation of neural structures is due to the actions of one or several stimuli, which are not adequate for many sensations. Attempts to identify the factors responsible for the activation of structures related to skin sensitivity are presented in a number of our studies [34, 36, 37, 49, 56, 57]. The goal of the studies was to determine which parameters of the ultrasound changed minimally when the threshold of tactile and thermal sensations appeared in the same sensitive points on the skin when ultrasound of different frequencies was used. The frequencies ranged from 0.48 to 2.67 MHz. The changes in some parameters of focused ultrasound (intensity, sound pressure, increment of temperature, displacement amplitude, and acoustic power) when the frequencies varied in the above-mentioned range for thermal and tactile sensations caused in the human fingers are shown in Fig. 6 [56]. The figure shows that there were considerable changes (sometimes within a few orders of magnitude) in some parameters of focused ultrasound. For example, the amplitude of the sound pressure varied approximately by a factor of 6, the temperature increased 100-fold, and the intensity increased by more than 30 times. The last value indicates that the radiation pressure, as a parameter characterizing, among other things, focused ultrasound in the focal region, should be excluded from consideration, since its magnitude is proportional to the intensity of ultrasound and changed significantly with changes in ultrasonic frequency. Formally, the amplitude of displacement (an alternating factor) was the most independent on the frequency. Although it seemed more logical if not an alternating but unidirectional mechanical effect of ultrasound related to demodulation of high–frequency ultrasonic oscillations appeared to be the most independent parameter [34, 49, 56, 57]. The radiation force, which is proportional to the acoustic power and in the linear approximation does not depend on frequency, could be this parameter. However, the existence of a direct correlation between the thresholds of tactile and thermal sensations and the magnitude of the acoustic power causes a question, why the threshold of the radiation force does not depend on the area of its application. Indeed, the focal spot area (32 mm^2 for the frequency of 0.48 MHz and 1 mm^2 for the frequency of 2.67 MHz) varied in our experiments by more than 30 times. This, however, did not have a significant effect on the threshold values of the radiation force.

A well-known mechanism of how shear waves with relatively high displacement amplitudes appear under the effect of radiation force was applied to explain this fact. In the study of A.P. Sarvazyan, O.V. Rudenko, et al. [59] it was shown that amplitude-modulated ultrasound with a carrier frequency of 3 MHz, modulation frequency of 1 kHz, the speed of shear waves in tissues of 3 m/s, and the intensity on the axis of ultrasonic beam of 10 W/cm^2, produced a displacement of about 30–40 μm in the tissue.

In [60], an expression for the maximum displacement in the medium $u_{\max}$ when using relatively short

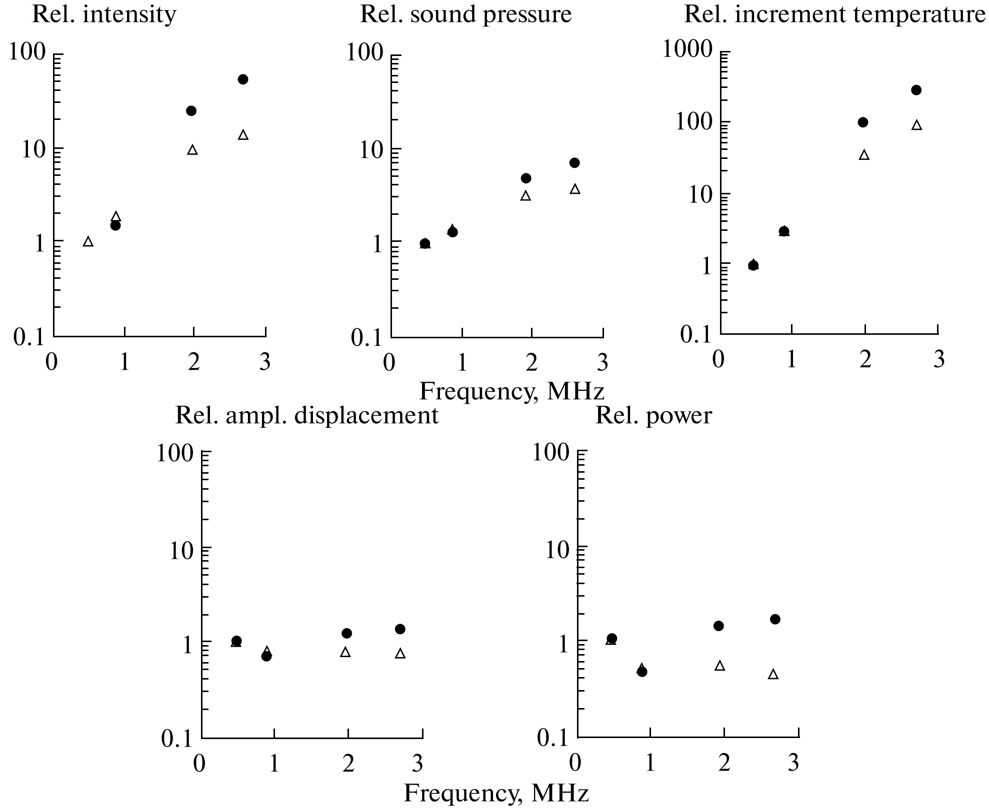

Fig. 6. Relative changes in the parameters of focused ultrasound (intensity, sound pressure, increment of temperature, displacement amplitude, and acoustic power) when the frequency changed from 0.48 to 2.67 MHz for tactile (triangles) and thermal (points) sensations in the human fingers.

pulses of focused ultrasound, the duration of which does not exceed the propagation time through the focal region, was obtained:

$$u_{\max} = \frac{\alpha a}{\rho c_l c_t} t_0 I \text{ for short pulses } (t_0 \ll a/c_t), \qquad (2)$$

where a is the radius of the sound beam (i.e., the radius of the focal region), α is the absorption coefficient of ultrasound in the medium, t_0 is the duration of the action of radiation force (i.e., the pulse duration), ρ is the density of the medium, c_t is the propagation speed of shear waves, c_l is the speed of longitudinal waves, and I and W are the intensity and acoustic power averaged over the pulse duration. From (2), it is evident that displacement under the action radiation force is proportional to $t_0 I$, i.e., it depends on the pulse energy more than on the intensity of ultrasound by itself.

In [57], this expression was modified for long pulses, when the pulse duration is longer than travel time through the focal region, which corresponds to the case under consideration. Then, the maximum amplitude displacement is

$$u_{\max} = \frac{\alpha}{\rho c_l c_t^2} a^2 I = \frac{\alpha}{c_l \mu} a^2 I = \text{const}\, W \qquad (3)$$
$$\text{for long pulses } (t_0 \gg a/c_t),$$

where W is the acoustic power averaged over the pulse duration and μ is the shear modulus of the medium, $c_t = \sqrt{\mu/\rho}$. Thus, the maximum amplitude of the displacement is proportional to the acoustic power and, hence, to the radiation force. A diagram illustrating the shape of the acoustic signal, the acoustic power, and shear displacement of the medium under the action of the ultrasonic pulse is shown in Fig. 7 [57]. One can see that the displacement of the medium (Fig. 7c) does not reproduce the shape of an acoustic signal (Fig. 7a), or acoustic power (Fig. 7b). The displacement reaches its maximum $u_{\max}$ after the time of propagation of shear waves through the focal region ($t_0 = a/c_t$). This time is relatively small, for example, for $a = 1$ mm and $c_t = 3$ m/s, it is $t_0 = 0.3$ ms, which is significantly shorter than the duration of an ultrasonic stimulus (usually from 1 to 100 ms). After this time, the magnitude of the shear displacement remains constant until the end of the pulse. This is consistent with our observation that pulses of the duration from 5–10 to 500 ms caused tactile sensations in response to the beginning and the end of a stimulus and that a subject under investigation could not distinguish one long pulse (for example, 400-ms duration) from two short pulses separated by the same time interval [34, 49]. These data support that stimulation of neural structures is related to the gradient of a stimulatory factor. In our case, it is a unidirectional displacement of the medium due to the radiation force. The proportionality between the maximal displacement of the medium and the acoustic power explains the above experimental data on the stimulation of structures caused by focused ultrasound of different frequencies.

Thus, the radiation force may be one of the factors responsible for the stimulatory effect of focused ultrasound. However, there is evidence that ultrasound has a direct stimulation effect on the fibers of the auditory nerve [15, 20]. In particular, the possibility of stimulating the fibers of the nerve auditory system using amplitude-modulated focused ultrasound was confirmed by experiments on a grass frog with a predestroyed receptor apparatus of the ear labyrinth [15]. Bioelectric responses to ultrasound stimulation similar in configuration to the responses to sound in the normally functioning receptor apparatus but with higher thresholds were registered in the auditory center of the midbrain. In addition, it was shown using special histochemical methods that, when the ear labyrinth was predestroyed, just the nerve fibers were activated [15]. Similar results of ultrasonic activation of the nerve fibers were obtained by recording the impulse activity in single afferents fibres of the limbs in rats under the action of focused ultrasound on the peripheral endings of these fibers in receptive fields of the soles [22, 23]. Finally, there were clinical observations at the Leningrad Institute of Ear, Nose, Throat, and Speech that some patients with full bilateral hearing loss confirmed audiologically were able to perceive auditory information transmitted by the amplitude-modulated focused ultrasound, while the usual hearing aids did not help them to hear [34].

Studies show that there are at least two factors responsible for stimulation of peripheral structures by focused ultrasound related to tactile and thermal sensations. The first of these factors is a unidirectional effect caused by the gradient of the shear displacement of the medium due to radiation force. The second factor is the direct action of focused ultrasound related, most likely, to the well-known biological effects of ultrasound, such as heating of tissues in some modes of exposure, oscillations of gas bubbles in biological media, and an increase in membrane permeability.

Mechanisms of pain sensations appearing under the effect of focused ultrasound include more relevant factors and require further studies.

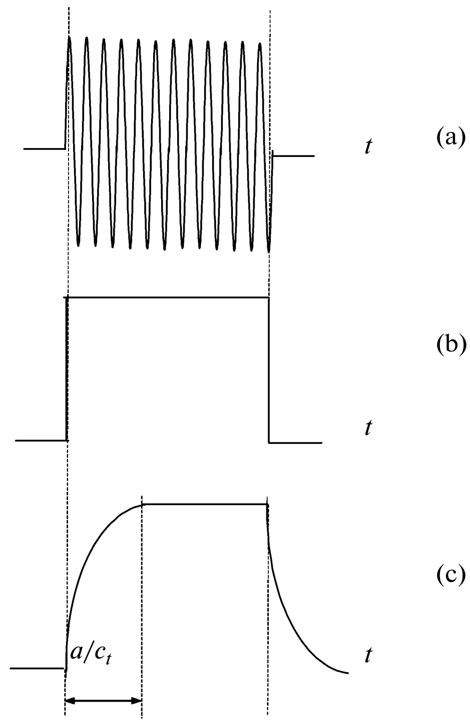

Fig. 7. Diagram illustrating the shape of an acoustic signal (a), acoustic power (b), and shear displacement of the medium (c) under the effect of an ultrasonic pulse.

IMPLEMENTATION OF ULTRASOUND STIMULATION

It was found that the thresholds of different sensations caused by focused ultrasound can be measured with high accuracy. On the other hand, a number of neurological and skin diseases, as well as hearing disorders, are accompanied by significant changes in sensitivity. By comparing the thresholds of various sensations caused by focused ultrasound in humans in normal and pathological states, one can make a diagnosis and assess the degree of pathological processes [34, 49, 61]. As an implementation of this approach, some diagnostic methods for several diseases related to the changes in the sensitivity of skin and tissues were developed. In particular, a study of the threshold sensitivity in the terminal phalanges of fingers in 30 neurological patients and 21 healthy humans (control group) was performed [61]. The diseases included syringomyelia, spondylogenic cervical radiculitis, residual effects of cerebral stroke, polyneuritis, ulnar and radial neuritis, etc. In all patients, increased tactile thresholds compared to the normal (up to entire absence of sensitivity under the maximum possible intensity of the stimulus) were found by means of studies using focused ultrasound. The observation of a number of patients with unilateral reduction in sensitivity is worth noting. They had increased thresholds not only in the damaged arm, but also in the symmetric parts of the skin of another arm that was considered healthy upon standard clinical examination. This effect was observed, in particular, in patients with syringomyelia [34, 61]. In some patients, pain in bones appeared under the effect of focused ultrasound, whereas, in healthy people, a stimulus of the same intensity did not cause any pain. It follows that, during some diseases, along with a reduction in tactile sensitivity (increased threshold), the thresholds of other sensations, such as pain, may decrease.

The method was successfully tested for estimating the regeneration of the bone tissue after fractures by measuring the dynamics of the pain thresholds in the periosteum. The normalization of the thresholds indicated successful bone regeneration.

The results of studies using the ultrasonic method of diagnosis of neurological diseases show its usefulness for medical applications. It is important that the proposed method ensures detection of subclinical stages of disorders of tactile sensitivity that cannot be detected by other methods. This possibility is particularly valuable for practical neurology.

In addition, diagnosis of skin diseases, such as psoriasis, atopic dermatitis, and scleroderma has been greatly facilitated [62] and the threshold of cutaneous pain in 64 patients with neurasthenia was measured. In the latter case, pain thresholds and adaptation to repeated stimuli were usually decreased in the patients [63].

The possibility of using focused ultrasound to study different types of pain related to deeply located neuroreceptor structures, such as the periosteum, is of particular interest. Recall that the sensations are evoked without direct contact of stimulating device with the structure and do not require preliminary invasive procedures [64].

The hearing thresholds when the ear labyrinth was affected by focused ultrasound modulated in amplitude by standard audiometric octave frequencies were measured. The differences between the standard threshold audiograms and audiograms measured by means of focused ultrasound at different hearing diseases were used as diagnostic criteria. The high efficiency of this method for diagnosis of hearing loss has been demonstrated in hundreds of patients [65]. It was also shown that the method is useful for selecting patients for electrode prosthesis.

Figure 4 shows that, by means of ultrasound focused at the ear labyrinth and modulated by pure tones, one can obtain a frequency-threshold curve (ultrasound audiogram) and, therefore, follow a procedure similar to audiometric determination of the thresholds of audibility of pure tones. The same as an audiogram, an ultrasonic frequency-threshold curve allows us to determine the hearing thresholds of modulation tones corresponding to the standard audiometric frequencies. The difference lies in the process of delivering the sound information to the ear labyrinth and in that different structures may be targets for the impact of sound stimuli and amplitude-modulated ultrasound. When using focused ultrasound, the path of ultrasonic waves to perceiving structures differs from the path of sound waves during the acoustic stimulation. By comparing tonal audiograms and ultrasonic frequency-threshold curves, one can obtain additional information about the functional state of the hearing organ. In addition to the method of tonal audiometry, the ultrasonic method for inputting auditory information may be used to diagnose diseases of the organ of hearing. This possibility was shown in several studies [49, 65–69]. Over 500 patients were examined in the Leningrad Institute of the Ear, Throat, Nose, and Speech. Frequency-threshold curves in subjects with normal hearing and patients with damaged auditory functions were compared. The curves obtained in patients differed significantly from their own audiograms. A clear correlation between the type of frequency-threshold curves and the nature of the disease was observed in patients, which were tested to diagnose various disorders of the auditory function. For example, otosclerosis is characterized by the absence of auditory sensation upon stimulation with one or more modulation frequencies of ultrasound (e.g., 125, 250, or 500 Hz), while sounds of the same frequencies are clearly heard by the patients. Various diseases also have a very characteristic configuration of ultrasonic frequency-threshold curves. In addition to otosclerosis, this fact was used to diagnose sensorineural hearing loss, acoustic neuroma, and other diseases [65–69].

With respect to the safety of the proposed methods, the values of ultrasonic parameters used were much less that those that cause morphological changes in tissues [34]. In addition, some indirect observations were made. So, during long-term study of skin and tissue sensitivity, almost every day, one of the continuous participants in this study was affected by focused ultrasound at the same sensitive point of skin of the arm. The intensity of ultrasound was tens, hundreds, and thousands of W/cm^2; the pulse duration was from 100 to 1 ms; and the ultrasound frequency ranged from fractions to units of megahertz. The stimuli were applied repeatedly, singly or in series. Neither changes in the threshold tactile or pain sensations were noted.

Similar results were obtained in the study of auditory perception of amplitude-modulated focused ultrasound by subjects with normal hearing. In these cases, the calculated ultrasonic intensity in the focal region was from units to tens of W/cm^2, the duration of exposure reaching several minutes at each session. No changes in the hearing sensitivity were observed several years after the participation of this person in the experiments. Moreover, none of the natural changes in auditory sensitivity sometimes occurring in people over 50 years of age were observed.

Let us consider the possibilities of audio prosthetics for the deaf using amplitude-modulated ultrasound. It is well known that 3–5% of the population in developed countries suffers deafness and impaired hearing. To fight against this disease, in addition to new types of surgery and drug treatment, improved models of hearing aids based on the principle of amplification of sound signals are being developed. However, the existing tools cannot help or are insufficient for a large group of practically deaf people. In order to help such patients, an attempt to use ultrasonic technique for audio prosthetics of the deaf was undertaken. In the 1980s, a few promising experiments in this area were carried out. For example, as already mentioned, some patients with full bilateral deafness perceived auditory information delivered by ultrasound, whereas standard hearing aids did not help them. We believe that ultrasonic audio prosthetics may be effective in cases of hearing loss or deafness with partial or complete loss of receptor elements, when the auditory nerve fibers, by which the auditory information is usually transmitted from hair cells to the brain, remain intact. At present, auditory prosthesis of such patients is carried out by implanting stimulating electrodes in a region with surviving auditory nerve fibers. In contrast to this method, the input of auditory information to the deaf using focused ultrasound is noninvasive and does not require complicated surgery.

The photographs of devices for diagnosis of diseases of hearing and audio prosthetics developed in the early 1980s in the Acoustic Institute and V.P. Vologdin Research Institute of High-Frequency Currents in cooperation with medical organizations are shown in Fig. 8. The “Sensofon” was the first of these devices (Fig. 8a). It is an ultrasound analogue of the tonal and speech audiometers. It has a relatively small size and weight and can be used in clinics. The device “Ultrafon” was designed for inputting auditory information to the deaf and hearing-impaired (Fig. 8b) is a simplified ultrasonic diagnostic device with a minimal number of external adjustments.

Obviously, the systems developed in the 1980s for research are cumbersome and are not comparable in size to the individual hearing aids used in conventional sound-amplifying audio prosthetics. In addition, it is still unknown whether a daily continuous—sometimes lasting for many hours—effect of focused ultrasound is harmless to the humans. It should be, however, noted that, during the first attempts to use an electrode prosthesis for the deaf, it was questionable how long patients could use the implanted electrodes. Now this is not disputed and the patients have been observed for decades. The problem of learning to use a prosthesis or an ultrasonic device for the highest-quality reception of auditory information is common to the electrode and ultrasonic prosthesis. Unfortunately, the studies described have been not implemented.

STUDIES IN THE 1990–2000s

Due to the general situation in our country at the beginning of the 1990s, which resulted in the termination of research funding, studies of functional effects of ultrasound in otology also stopped. The works on the application of focused ultrasound for studying the skin and tissue sensitivity were also significantly reduced. During the 1990–2000s, in the Institute of Evolutionary Physiology and Biochemistry and the Acoustics Institute, studies were carried out in an informal way, by the efforts of a few enthusiasts.

Fig. 8. Devices for diagnosis of hearing diseases and studying the possibilities of inputting auditory information to the deaf.

However, in these years, the study of functional effects of ultrasound was developed in some foreign laboratories [70–73]. It was shown that single pulses of focused ultrasound can significantly modify the excitability of the myelinated nervous fibers of the sciatic nerve of a frog (*in vitro*) during 40–50 ms after the termination of the pulse [70, 71]. The modification consisted of both intensification and depression of excitability. Focused ultrasound with a frequency of 2.7 MHz was applied in a pulsed mode with pulse duration of 0.5 ms and a peak intensity of 100–800 W/cm^2. The authors explained the changes in excitability of the fibers of the sciatic nerve by the action of radiation pressure, but not by the action of the temperature, since the calculated temperature rise after each pulse was only 0.025°C.

Focused ultrasound was also used to modify evoked potentials and the functioning of local nerve circuits in the mammalian brain [72, 73]. The samples of rat hippocampal preparations *in vitro* were used as an object of studies. The extracellular evoked potentials were studied. Under the effect of pulses of focused ultrasound with a frequency of 500 kHz at a repetition frequency of 200 kHz and intensities of 50–140 W/cm^2, the evoked potentials were in some cases increased; in other cases, they were suppressed. According to the authors, this effect is caused by a superposition of mechanical and thermal effects. In their view, a clearer understanding of the true mechanism of stimulatory and inhibitory action of ultrasound of brain structures is very important for further development of the ultrasonic method in neurophysiological research and in clinics. If this mechanism were to become clearer, then there would be the possibility of achieving the necessary effects in the living organism, as well as creating reversible inhibition and temporary stimulation in the specified regions of the brain by means of manipulating the ultrasound parameters. According to the authors, it would be an invaluable noninvasive tool for studying the functions of the normal brain by reversible supression or stimulation of small parts of it. In addition, it would open new opportunities for application of ultrasound in medicine.

In a study performed at the University of Rochester [74], tactile sensations were evoked by a nonfocusing ultrasonic radiator with a plastic disc that was mounted on the skin of a subject and prevented the passage of ultrasound in tissues. Single ultrasonic stimulus with duration of 5–100 ms, and a series of pulses at a repetition frequency from 50 to 1000 Hz were used. Radiation force was considered the main factor responsible for the emergence of tactile sensations. In the case of using single pulses, the thresholds of radiation force necessary for the emergence of tactile sensations in subjects with normal skin sensitivity varied in the range of 1–2 G [74]. In the case of applying series of pulses it was an order of magnitude smaller. The thresholds did not significantly change in the presence of the plastic disk and its absence, that is, with or without direct action of ultrasound on the skin. The important difference between this approach and that described above was that, in our research, focused ultrasound affected tissues, including deep ones, directly; whereas, in the cited study [74], a direct effect of ultrasound was eliminated.

The stimulatory effect of focused ultrasound and, in particular, its ability to cause threshold and near-threshold pain in the skin and underlying tissues of humans was studied at Queen's University in Belfast, Northern Ireland, United Kingdom. Researchers attempted to assess the analgesic effect of pethidine by measuring pain thresholds in the joints before and after taking medicine using pulses of focused ultrasound. A progressive decrease in the amplitude of evoked potentials for 3.5 h after taking pethidine [75] was found. In the mid-1990s, cooperation between the Sechenov Institute of Evolutionary Physiology and Biochemistry, the Acoustics Institute, and the University in Belfast, was facilitated by two Grants of the Royal Society of Great Britain, which resulted in joint studies and publications on the use of focused ultrasound as a stimulator of neuroreceptor structures [24, 56, 64]. In particular, by means of focused ultrasound, certain types of cutaneous pain were found in humans and characterized [24]. Later, it was shown that cutaneous and previously described [76] articular pain caused by ultrasound have identical characteristics of evoked potentials and eye movements [25].

The phenomenon of temporal summation of pain arising under the action of focused ultrasound in the skin, muscle tissue, and joints has been studied in human beings [77]. The ultrasonic frequency was 1.66 MHz; the pulse duration varied from 25 to 100 ms. Single stimuli and a sequence of five stimuli at different repetition rates (from 0.5 to 5 Hz) were used. Temporal summation was found for skin, muscle, and joint pain; however, it was better expressed in muscle pain. A higher intensity of ultrasound was necessary to evoke pain in muscle tissue than for cutaneous and articular pain.

In was found in a completely different field of study that pulsed ultrasound generated by diagnostic ultrasonic systems can stimulate fetal movement (for 25–40 weeks of pregnancy) [78]. When pulsed modes (Doppler and B-scan) of ultrasound were applied, the number of movements per minute was nine times more than in the control group (without an impact) and almost six times more than that for the Doppler scanning in a continuous mode. The authors suggested that this effect is due to the action of the radiation force of ultrasound, because the pulse repetition frequency in most diagnostic systems ranges from 1 to 10 kHz, i.e., is in the audible frequency range. In addition to an increase in the frequency of fetal movements, the authors registered a slight increase in the fetal heart rate. The patent obtained by this laboratory [79] is based on the stimulating a fetus with an amplitude-modulated ultrasonic signal with a frequency of 1–10 MHz. In regard to this study, note the studies on the sensitivity of the fetus to acoustic waves with frequencies from 4 to 24 kHz coming through the wall of the mother's abdomen that were carried out at the Sechenov Institute of Evolutionary Physiology and Biochemistry in cooperation with the D.O. Ott Institute of Obstetrics and Gynecology in the mid-1990s [80]. The reactions of the fetus did not differ from the results of above-described ultrasonic study [78] and from vibroacoustic testing [80], which gives reason to assume that these studies for determining the presence of hearing in the fetus using amplitude-modulated ultrasound need in development. If these works are successful, then it will be possible to determine the condition of hearing in a fetus before birth during routine ultrasonic examination of pregnant women with visualization of a fetus, which is compulsory in many countries.

Researchers from Taiwan have studied the effect of ultrasound on the conductive properties of bullfrog sciatic nerve fibers *in vitro* [81]. Ultrasound with a frequency of 3.5 MHz and an acoustic power of 1–3 or 5 W was applied for 5 min. The amplitude of evoked potentials and the velocity of nerve impulses before and after the ultrasound treatment were measured. The velocity of nerve impulses increased by 5–20% at acoustic powers from 1–3 W. The amplitude of evoked potentials increased by 8% during stimulation with an acoustic power of 1 W; however, it significantly decreased at powers of 2 and 3 W. The authors connected this inhibitory effect with the thermal action of ultrasound.

In [82], the influence of some parameters of focused ultrasound (intensity and duration of exposure) on the conductivity of the sciatic nerve in rats was studied *in vivo*. The goal was to determine the doses required for partial and full blocking of the nerve conduction and, thus, to determine the possibility of using ultrasound as an alternative to current clinical methods for blocking the nerve conductivity. Focused ultrasound with a frequency of 5.7 MHz with peak intensities from 390 to 7890 W/cm^2 was applied for 5 s. Evoked responses of the muscles to the electrical stimulation of the nerve in combination with the ultrasonic effect were recorded in the muscle tissue of the sole before and immediately, 2, and 4 h after ultrasonic treatment. In the range of intensities from 390 to 3300 W/cm^2, the amplitude of the responses was reduced from 4 h to 7 days after the exposure and returned to its original value 28 days after the treatment. For the maximal intensity of 7890 W/cm^2, the responses were absent 28 days after the treatment. The authors believe that their data may be useful when using a powerful focused ultrasound for treatment of severe muscle pain and spasticity (i.e., involuntary muscle tension).

The studies of R. Muratore et al. [83, 84] are devoted to the possibility of inducing functional changes in the neuronal cells using small doses of ultrasound. The objects of studies were cells of PC12 line *in vitro* obtained in rat. To affect the culture of cells, pulses of focused ultrasound with a frequency of 4.67 MHz, duration of 0.1 ms, and amplitude of 100 kPa were used. To control the functional changes, the cell culture from the hippocampus of the rat affected by the pulses of focused ultrasound with a frequency of 4.04 MHz, duration of 0.1 ms, and amplitude of 77 kPa was used. Before and after ultrasound treatment, the culture was stimulated using biphasic stimuli of 100 mA electrical current with a duration of 0.1 ms. Optical microscopy showed that, under the effect of ultrasound, PC12 cell cultures grouped in the focal region elongated to about 2 mm and, after termination of the effect of ultrasound, they returned back to their original shape. The authors suggest that deformation of cells in the culture is due to the action of the radiation force. In the second culture, both electrical and ultrasonic stimuli lead to two-phase responses that are identical in shape. Furthermore, according to the electrical responses, after ultrasound treatment, the culture remained viable. The authors believe that their experiments showed that ultrasound in small doses can stimulate the neurons; however, the mechanism of the effect remains unknown. In [83], it is noted that the threshold amplitude of the ultrasonic stimulus necessary for the emergence of this effect is 20–48 kPa. However, simple estimations show that the metrology of these very interesting studies should be carefully checked. Since the focused ultrasound had a rather high frequency (more than 4 MHz) and the calculated radius and the area of the focal spot were 1 mm and 0.03 cm^2, respectively, the values of acoustic power and radiation force were extremely small (respectively, about 0.0015 watts and 0.1 mg). It is hard to believe that such values of the radiation force could cause the well-observed functional effects.

It was shown using culture of hippocampal slices of mouse brain that ultrasound with a low frequency (0.67 MHz or less) and low intensity (300 mW/cm^2) can cause the appearance of action potentials and synaptic excitation transfer [85].

The possibility of using focused ultrasound for blocking nerve conductivity in order to control pain and create local anesthesia was studied in Boston [86]. The sciatic nerve of bullfrog *in vitro* in a Ringer's solution was used as the object of study. Action potentials were recorded during electrical stimulation of the nerve and repeatedly recorded after the effect of focused ultrasound with frequencies of 0.661 and 1.986 MHz on the nerve. The action potential decreased, which correlated with an increase in temperature measured in the nerve. Depending on the parameters of the ultrasonic impact, action potentials recovered fully, partially, or not at all. Cooling of the liquid that surrounded the nerve did not prevent blocking the action potentials; however, more powerful ultrasound was needed to achieve the effect of blocking than that without cooling. This means that constant or temporary thermal action is required for blocking of the nerve. This finding coincides with previous data [9, 10]. According to the authors, when focused ultrasound of high frequencies is used, there is no need to search for explanations of the effects obtained by any other reasons, besides the heat. However, when lower frequencies are used, some other non–thermal mechanism is expected to participate. This mechanism is not completely clear; it may be related to the activity of cavitation bubbles in that particular experimental conditions. In the conditions *in vivo*, this effect may not occur.

The possibility of using focused ultrasound for treatment of epilepsy artificially induced in rats by means of special chemicals was studied in [87]. The diameter of the radiator was 6 cm, the radius of curvature was 7 cm, and the ultrasonic frequency was 690 kHz. Ultrasound pulses with a duration of 0.5 ms with a repetition frequency of 100 Hz and intensity of 130 mW/cm^2 were used. The animal's brain was affected through the skull twice for 3 min, and an electroencephalogram (EEG) was recorded. The deviations in the EEG related to epilepsy rapidly decreased after the effect of ultrasound; behavioral reactions changed in a positive direction as well. Histological analysis confirmed the absence of damage in the brain tissues. According to the authors, low-intensity ultrasound in a pulse mode can be used for noninvasive treatment of epilepsy. A hypothetical possibility of treatment of epilepsy in humans by using focused ultrasound, which the authors believe to be an ideal tool for neuromodulation of the brain structures, is considered in [88].

In the studies of the Sechenov Institute of Evolutionary Physiology and Biochemistry [89], during EEG recording, electrical responses of the brain to stimuli of focused ultrasound inducing auditory and tactile sensations and skin pain, as well as to sound stimuli that cause auditory sensations, were obtained. Responses that were characteristic for all stimuli were determined. In particular, it was shown that the simultaneous effect of sound and ultrasonic stimuli that caused, respectively, auditory and tactile sensations increased the amplitude of the response compared with the answer to any one of these stimuli without changing its latency. Experiments with focused ultrasound and the following experiments with adequate stimuli first showed that sensations of different modalities (tactile, thermal, hearing, etc.) are accompanied by nistagmoid eye movements [89]. These movements are more noticeable when using ultrasonic stimulation as compared to adequate stimuli. The latency and amplitude of eye movements depended on the strength and duration of stimulation by focused ultrasound. The continuation of the described studies is promising.

The possibilities for implementation of ultrasonic stimulation of neuroreceptor structures increased significantly after the appearance of two-dimensional phased arrays that generate focal areas of complex configuration and, therefore, affect many structures simultaneously. This possibility is of particular interest in connection with the development (primarily in Japan) of tactile-based methods and systems for robotics, sensors, and control systems, as well as human–machine interfaces. Tactile displays for information transfer by the acoustic method based on the effect of radiation pressure are promising [90–92]. Such a display is needed to create rapidly changing images, especially images with a complex configuration (geometric figures, symbols, letters, etc.). For this purpose, the authors of these works developed a two-dimensional tactile display, the changes in the acoustic field at the surface of which were performed using a single focus that moved in two mutually perpendicular directions [92]. To generate the focus and move it in the plane of the display, a focusing system, which was a combination of eight linear phased arrays, was used. The results of computer simulation of the acoustic field generated by this system showed that the intensity in the secondary maxima was 13% of the maximum intensity in the focus, even for the case in which the focus was located on the acoustic axis of the system. In the case of moving the focus off the axis, the intensity of the secondary maxima will inevitably be considerably greater than the above-mentioned value. Thus, the quality of an acoustic field produced by the described focusing system requires significant improvement. Another drawback of the system is that it is designed to move only one focus on the surface of the display at a time.

An alternative way to create similar tactile displays based on the use of a two-dimensional phased array with randomly distributed elements on the array surface was proposed and studied in numerical model experiments at the Acoustics Institute [93]. It was shown that the use of such arrays makes it possible to synthesize symbols with complex shapes, in particular the letters of the alphabet. The distributions of intensity in the focal plane corresponding to the two letters S and W are shown in Fig. 9 [93]. To create these symbols, 24 and 25 foci, respectively, were used. The sizes of the fields where the simulations were carried out were 4×4 (a) and 1×1 cm (b). The absence of significant secondary maxima within the field indicates comprehensible quality of the intensity distributions.

In connection with the images presented in Fig. 9, it is worthwhile to consider another possible application of ultrasonic stimulation of nerve structures. There are tactile displays allowing blind and even deaf-and-blind persons to perceive textual information displayed by a relief-dot font due to the effect of the radiation pressure. Small pins which rise and fall in order to form a symbol are commonly used in these devices. Letters are depicted in Braille system, which allows the equivalent of a printed symbol to be created using six to eight dots. To depict symbols in Braille is much easier than the letters of the Latin or Cyrillic alphabet. However, such displays have drawbacks and limitations. The devices in which the pins are moved mechanically are noisy and require direct contact between the skin of the subject and the pins, and the speed of the image on the display is very limited. Ultrasonic tactile displays have potential advantages: they are noiseless, contactless, and provide a high update rate on the display. Symbols with a complex configuration (letters, digits, punctuation, etc.) may be created on the display. Although the feasibility of implementing ultrasonic displays to present printed symbols on the display rather than their equivalents in Braille is the subject of separate study, the technical possibility of creating such devices has been proven [93].

The authors of [94] believe that the use of multielement phased arrays is very promising for generating multifocus affecting regions with complex configurations in order to activate and change the functional

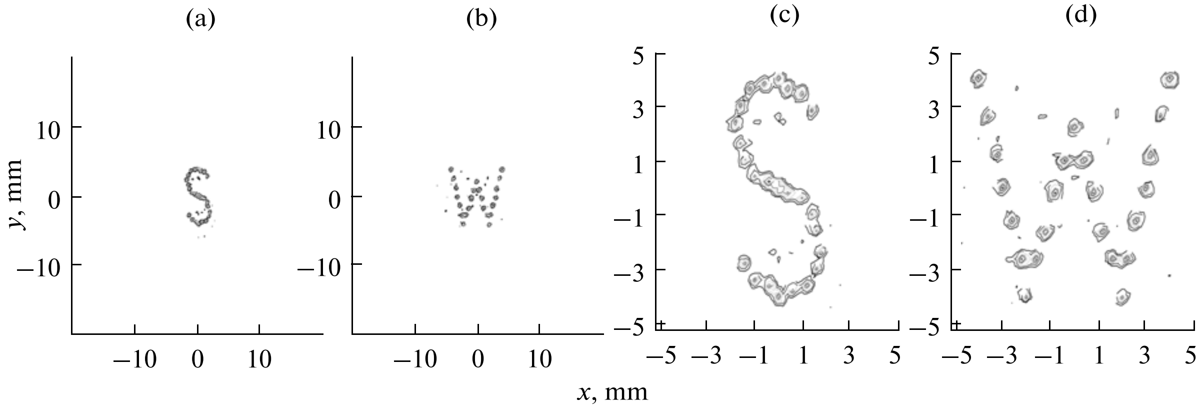

Fig. 9. Synthesis of complex symbols in the shape of some letters of the alphabet using a randomized phased array. The dimensions of the investigated field were 4 × 4 (a, b) and 1 × 1 cm (c, d).

state of different neural structures. To create appropriate devices and systems, the authors developed effective and fast algorithms for calculating the phase of the elements on the array necessary for the generation of multifocus ultrasonic fields with given parameters of foci. Thus, studies [93, 94] suggest that technical challenges to the creation of ultrasound systems for activation of nerve structures by means of multifocus ultrasonic fields largely have been overcome. However, as shown in this review, implementation of high-grade managing the functions of the human central nervous system using focused ultrasonic stimuli has not yet been achieved.

OUTLOOK: REALITY AND PROSPECTS

Let us list some of the most promising possibilities of using focused ultrasound for functional effects on neuroreceptor structures or, in other words, for inputting information through different sensory channels. Many of them remain unimplemented. As already mentioned, by the late 1980s, there were at least two very promising areas of implementation of the functional ultrasonic effect on neuroreceptor structures. The first was related to activation of the structures of the somatosensory system. It contained specific areas, such as ultrasonic medical diagnosis, based on measurement of thresholds for different sensations in patients with various pathologies compared to normal thresholds. This method was used for diagnosis and prognosis of some neurological and skin diseases.

Another important area for implementation of focused ultrasound as a stimulus is related to the diagnosis of hearing diseases and input of auditory information for people with hearing disabilities up to total deafness. In addition, ultrasonic testing can be used for selection of patients the auditory functions of whom could be improved after electrode hearing prosthesis.

Ultrasound is promising in physiological studies for examining the possibilities of functional effects on the visual, olfactory, taste, and other sensory systems of humans and animals, as well as in studies of thermoreception mechanisms, heat production, and thermoregulation using focused ultrasound. Studying deep pain and searching for methods of pain relief in individual organs and tissues using ultrasound treatment is promising. In addition, it is unquestionable that studies of the direct functional effects of ultrasound on the central nervous structures and neuroreceptor structures should be continued.

Let us formulate the basic physiological findings obtained in studies using ultrasound.

(1) Ultrasound can activate not only peripheral neuroreceptor structures, but also nerve fibers, and it can have a functional effect on brain structures.

(2) Temperature, tactile, and aural reception should be regarded as mechanoreception.

(3) Sensations of heat and cold depend on the activation of the same nerve fibers.

(4) Cutaneous pain is related to specific (mostly for pain) or nonspecific (for pain and other skin sensations) afferent nerve fibers.

(5) The application of focused ultrasound first showed that different sensory modalities are associated with nistagmoid eye movements (that was then confirmed by responses to adequate stimuli).

Studies show that the implementation of focused ultrasound as a stimulator of neuroreceptor structures is most promising in the following areas.

(1) Diagnosis based on the measurements of thresholds of sensations.

(2) Prosthesis of various sensory functions, such as auditory function.

(3) Selection of patients, the auditory function of which can be substantially improved by means of electrode (electroimplantation) prosthesis.

(4) Pain relief and therapy of various diseases by ultrasound effects on neuroreceptor structures, such as acupuncture points or painful regions.

(5) Evaluating the effectiveness of analgesic medicines by measuring pain thresholds before and after use.

(6) Investigation of the temperature sensitivity and the diagnosis of its disorders.

(7) Prenatal diagnosis of hearing disorders in the fetus by means of amplitude-modulated ultrasound, which could be carried out during routine ultrasonic examination during pregnancy.

(8) Using two-dimensional phased arrays for activation of neuroreceptor structures.

Other possible uses of ultrasound and promising directions for further research were discussed in the review [56]. Note that the current level of electronics allows to create portable generators to supply the focusing ultrasonic radiators for applications in medicine. For example, as was reported in [95, 96], a powerful ultrasonic generator with a very low output impedance (0.05 Ω) was developed. It can transmit 99% of the energy from a power supply to an ultrasonic transducer. The acoustic power at a transducer with a frequency of 1.54 MHz is more than 130 W, and no matching with it is required. The small size of the device (an area of 5×8 cm), high power and efficiency, and ability to operate over a wide frequency range (up to 10 MHz) allow using the device in a great variety of areas, including medicine.

Although there are already many feasible and useful applications of focused ultrasound for functional effects on neuroreceptor structures, “sensationalist” ideas and approaches that do not take into account the long-term experience of previous studies are increasingly appearing in the worldwide literature and in the mass media. Thus, in recent years, attempts to use a direct effect of focused ultrasound on the human brain to activate the central nervous structures unexpectedly increased. For example, Sony Corp. and Sony Electronics have patented a method and a system for inputting information into the human brain [97]. The invention consists of a method and apparatus for stimulating certain areas of the human brain by focused ultrasound to cause different sensations, such as auditory, visual, and taste. The device is based on the use of a phased array that stimulates certain areas of the cerebral cortex by focused ultrasound. Ultrasound transducers are located inside a helmet, following its configuration, and are in contact with the tissues of the head. According to the authors of the patent, ultrasonic pulses change the state of neural fields, causing users to experience tactile sensations, smell odors, hear sounds, and see graphic images presynthesized by a computer. One of the goals of the patent was to return the vision and hearing to blind or deaf patients, respectively. It should be noted that a Sony Electronics spokeswoman has said (New Scientist, Vol. 2494, April 7, 2005, p. 10) that the work is speculative. “There were not any experiments done,” she says. “This particular patent was a prophetic invention. It was based on an inspiration that this may someday be the direction that technology will take us”.

Projects related to the use of ultrasound for activating the functional effects on the nervous structures of the brain and claiming to be sensational were performed most recently in the United States. The goal of these projects was to cause the stimulation of brain structures using low doses of ultrasound at relatively low frequencies [98, 99]. The media have reported that the laboratory of Dr. Tyler at Arizona State University is developing neuromodulation techniques such as deep brain stimulation through the skull bone. It is assumed that the ultrasonic dose required for these effects should be significantly less than that used for ultrasonic imaging of tissues. According to the developers, the technology could be useful in treating various neurological diseases and for military purposes, such as pain relief immediately on the battlefield in the case of injuries, as well as in computer games, for memory control, entertainment, etc.

Some grounds for the proposed technology were given by experiments in which the cerebral cortex of rats was affected by short pulses of ultrasound, which caused motor responses. These effects were observed at very low intensities averaged over time (40–60 mW/cm^2) in the frequency range from 0.35 to 0.5 MHz [98]. Under the effect of ultrasonic pulses (in beams with different diameters) on the motor domain of rat brain through intact skull, there was an increase in the frequency of spontaneous impulse activity of the head, which could hypothetically be related to both the activity of nerve cells in the motor domain of the brain, or to the head’s muscles [98]. It was impossible to separate reliablly the activities related to the nerve cells and muscles or to determine the dependence of the activity on the diameter of an ultrasonic beam and the projection of the beam to the brain. As a result, no convincing evidence of the appearance of ultrasound-induced impulse activity of brain cells was shown in this paper. It is clear that the path from the preliminary experiments described to the final goal of the authors (managing the functions of the central nervous system) is very long and its eventual success is in doubt.

Nevertheless, the work of several groups in different countries studying the functional (mostly stimulating) effect of ultrasound on the peripheral and central neuroreceptor structures allows to hope for important new results in this area [25, 82–84, 86, 87, 98, 100–103].

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