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LOW-INTENSITY TRANSCRANIAL FOCUSED ULTRASOUND NEUROMODULATION: MECHANISMS, CLINICAL APPLICATIONS, SAFETY, AND FUTURE DIRECTIONS

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Abstract

Background. Low-intensity transcranial focused ultrasound is an emerging noninvasive neuromodulation technology capable of targeting cortical and deep cerebral structures with greater spatial selectivity than conventional electrical or magnetic stimulation. Unlike high-intensity focused ultrasound, it is intended to modify neural activity without producing permanent tissue ablation.

Materials and methods. A concise narrative review was conducted using experimental studies, early clinical trials, technical investigations, and international reporting and safety recommendations. Evidence was evaluated according to biological mechanism, acoustic parameters, target engagement, clinical applicability, safety, and reproducibility.

Results. Ultrasound may influence neuronal activity through acoustic radiation force, membrane deformation, mechanosensitive ion channels, synaptic modulation, and neurovascular mechanisms. Human studies demonstrate modulation of the motor cortex, thalamus, basal ganglia, hippocampus, amygdala, and distributed functional networks. Preliminary therapeutic applications include Parkinson's disease, drug-resistant epilepsy, depression, disorders of consciousness, chronic pain, and post-stroke rehabilitation. However, clinical studies remain limited by small samples, heterogeneous sonication protocols, variable sham conditions, skull-related acoustic distortion, and insufficient long-term follow-up.

Conclusion. Low-intensity focused ultrasound provides a promising platform for reversible and anatomically precise neuromodulation. Nevertheless, it remains predominantly investigational. Individualized acoustic modeling, standardized dose reporting, credible sham control, objective target-engagement biomarkers, and multicenter validation are required before routine clinical implementation.

Keywords: focused ultrasound, transcranial ultrasound stimulation, neuromodulation, deep brain stimulation, acoustic modeling, neuroplasticity, neurological disorders.

НИЗКОИНТЕНСИВНАЯ ТРАНСКРАНИАЛЬНАЯ ФОКУСИРОВАННАЯ УЛЬТРАЗВУКОВАЯ НЕЙРОМОДУЛЯЦИЯ: МЕХАНИЗМЫ, КЛИНИЧЕСКОЕ ПРИМЕНЕНИЕ, БЕЗОПАСНОСТЬ И ПЕРСПЕКТИВЫ

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Аннотация

Актуальность. Низкоинтенсивный транскраниальный фокусированный ультразвук представляет собой развивающуюся технологию неинвазивной нейромодуляции, позволяющую воздействовать на корковые и глубокие структуры головного мозга с более высокой пространственной избирательностью по сравнению с традиционной электрической или магнитной стимуляцией. В отличие от высокоинтенсивного фокусированного

ультразвука, метод предназначен для изменения нейронной активности без формирования необратимого очага абляции.

Материалы и методы. Проведен краткий нарративный обзор экспериментальных исследований, ранних клинических испытаний, технических работ и международных рекомендаций по стандартизации и безопасности. Доказательства оценивались по механизму действия, акустическим параметрам, вовлечению мишени, клинической применимости, безопасности и воспроизводимости.

Результаты. Ультразвук может воздействовать на нейронную активность посредством акустической радиационной силы, деформации клеточных мембран, механочувствительных ионных каналов, синаптической модуляции и нейроваскулярных механизмов. Исследования у человека подтвердили возможность модуляции моторной коры, таламуса, базальных ганглиев, гиппокампа, миндалевидного тела и распределенных функциональных сетей. Предварительные направления применения включают болезнь Паркинсона, фармакорезистентную эпилепсию, депрессию, нарушения сознания, хроническую боль и постинсультную реабилитацию. Однако доказательная база ограничена небольшими выборками, неоднородными протоколами, несовершенным плацебо-контролем и недостаточным длительным наблюдением.

Заключение. Низкоинтенсивный фокусированный ультразвук является перспективной платформой обратимой и анатомически точной нейромодуляции, однако пока остается преимущественно экспериментальным методом. Для клинического внедрения необходимы индивидуальное акустическое моделирование, стандартизированное дозирование, объективные биомаркеры вовлечения мишени и многоцентровая валидация.

Ключевые слова: фокусированный ультразвук, транскраниальная ультразвуковая стимуляция, нейромодуляция, глубокая стимуляция мозга, акустическое моделирование, нейропластичность, неврологические заболевания.

PAST INTENSIVLIKDAGI TRANSKRANIAL FOKUSLANGAN ULTRATOVUSH NEYROMODULYATSIYASI: MEXANIZMLAR, KLINIK QO‘LLANILISHI, XAVFSIZLIGI VA ISTIQBOLLARI

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Annotatsiya

Dolzarblik. Past intensivlikdagi transkranial fokuslangan ultratovush an’anaviy elektr yoki magnit stimulyatsiyaga nisbatan bosh miyaning kortikal hamda chuqur tuzilmalariga yuqori fazoviy aniqlikda ta’sir ko‘rsatishga imkon beruvchi rivojlanayotgan noinvaziv neyromodulyatsiya texnologiyasidir. Yuqori intensivlikdagi fokuslangan ultratovushdan farqli ravishda, ushbu usul qaytmas ablatsion o‘choq hosil qilmasdan neyron faolligini o‘zgartirishga mo‘ljallangan.

Material va usullar. Eksperimental tadqiqotlar, dastlabki klinik sinovlar, texnik izlanishlar hamda standartlashtirish va xavfsizlikka oid xalqaro tavsiyalar asosida qisqa narrativ sharh o‘tkazildi. Dalillar biologik mexanizm, akustik parametrlar, nishon tuzilmasining faollashuvi, klinik qo‘llanilish, xavfsizlik va takrorlanuvchanlik bo‘yicha baholandi.

Natijalar. Ultratovush akustik radiatsion kuch, hujayra membranasining deformatsiyasi, mexanik ta’sirga sezgir ion kanallari, sinaptik modulyatsiya va neyrovaskulyar mexanizmlar orqali neyron faolligiga ta’sir qilishi mumkin. Insonlarda motor korteks, talamus, bazal gangliyalar, gippokamp, amigdala va funksional neyron tarmoqlarni modulyatsiya qilish imkoniyati ko‘rsatilgan. Dastlabki klinik yo‘nalishlar Parkinson kasalligi, farmakorezistent epilepsiya, depressiya, ong buzilishlari, surunkali og‘riq va insultdan keyingi reabilitatsiyani qamrab oladi. Biroq dalillar kichik tanlanmalar, turlicha sonikatsiya protokollari, yetarli bo‘lmagan soxta nazorat va qisqa kuzatuv bilan cheklangan.

Xulosa. Past intensivlikdagi fokuslangan ultratovush qaytar va anatomik jihatdan aniq neyromodulyatsiya uchun istiqbolli platformadir. Klinik amaliyotga joriy etishdan oldin individual akustik modellashtirish, standart dozalash, obyektiv biomarkerlar va ko‘p markazli validatsiya talab etiladi.

Kalit so‘zlar: fokuslangan ultratovush, transkranial ultratovush stimulyatsiyasi, neyromodulyatsiya, chuqur miya stimulyatsiyasi, akustik modellashtirish, neyroplastiklik, nevrologik kasalliklar.

Introduction. Neuromodulation has become an important component of functional neurosurgery and clinical neuroscience. Deep brain stimulation can provide sustained improvement in selected movement disorders, epilepsy, obsessive-compulsive disorder, and other neurological conditions, but it requires intracranial electrode implantation and long-term hardware management. Transcranial magnetic stimulation and transcranial electrical stimulation are noninvasive, although their capacity to target small deep structures remains limited. Low-intensity transcranial focused ultrasound, also termed transcranial ultrasound stimulation, uses focused acoustic waves to alter neural activity without creating a permanent lesion. It must be distinguished from high-intensity magnetic resonance-guided focused ultrasound, which produces thermal coagulation and is used for ablative procedures such as thalamotomy or pallidotomy. Low-intensity stimulation is intended to produce reversible or plasticity-related neurophysiological effects while preserving tissue structure [1, 2, 3]. The principal theoretical advantages of the technology are deep penetration, millimeter-scale targeting, compatibility with individualized neuroimaging, and the possibility of repeated treatment. These properties create opportunities for noninvasive interrogation of neural circuits that previously required implanted electrodes.

Materials and Methods. A concise narrative review was performed using experimental studies, early-phase human investigations, technical validation studies, and international consensus recommendations published through July 2026. The review focused on nonablative ultrasound neuromodulation and excluded thermal lesioning and microbubble-mediated blood–brain barrier opening except where comparison was required. The evidence was analyzed in relation to the proposed biological mechanism, stimulation parameters, skull transmission, target accuracy, clinical applications, safety, and methodological limitations. Because the clinical literature remains heterogeneous, findings were interpreted as preliminary unless replicated in controlled studies.

Mechanisms of Ultrasound Neuromodulation. The precise biological mechanisms of ultrasound neuromodulation remain incompletely defined. Acoustic radiation force may produce microscopic displacement and deformation of neuronal membranes. These mechanical effects can alter membrane capacitance and influence mechanosensitive ion channels, voltage-gated channels, synaptic vesicle release, and intracellular calcium signaling. Other proposed mechanisms include modulation of inhibitory and excitatory neurotransmission, astrocytic activity, neurovascular coupling, and local network synchronization. Small temperature changes may contribute under some exposure conditions, although clinically intended low-intensity protocols are designed to remain below thresholds associated with thermal ablation [3, 6, 10]. The direction of the neurophysiological effect is not determined by intensity alone. Carrier frequency, pulse duration, pulse-repetition frequency, duty cycle, acoustic pressure, sonication duration, intertrain interval, target characteristics, and baseline neural state can influence whether the resulting effect is predominantly excitatory, inhibitory, mixed, or undetectable. Theta-burst ultrasound protocols may induce effects that persist after stimulation, suggesting modulation of synaptic plasticity. However, parameter-response relationships are not yet sufficiently standardized to permit direct transfer of a protocol from one cerebral region or disease to another [5, 11, 16].

Table 1. Principal parameters of transcranial ultrasound stimulation

Parameter	Functional significance
Carrier frequency	Influences skull penetration, attenuation, wavelength, and focal dimensions
Acoustic pressure	Determines the magnitude of mechanical exposure
Pulse duration	Influences temporal integration of the acoustic effect

Pulse-repetition frequency	Defines the interval between successive acoustic pulses
Duty cycle	Represents the proportion of time during which ultrasound is active
Sonication duration	Determines cumulative exposure during one stimulation train
Intertrain interval	May influence facilitation, inhibition, or neural adaptation
Focal dimensions	Determine anatomical selectivity and off-target exposure
Skull-adjusted intensity	Estimates the actual intracranial dose more accurately than free-field output
Thermal and mechanical indices	Contribute to biophysical safety assessment

Targeting and Acoustic Modeling. The skull represents the main technical barrier to reliable transcranial ultrasound delivery. Bone absorbs, reflects, refracts, and distorts acoustic waves. Skull thickness, density, curvature, internal composition, target depth, angle of incidence, and transducer frequency differ substantially among individuals. Consequently, the electrical output of the ultrasound device does not directly represent the dose delivered to the brain. Computed-tomography-based acoustic modeling can estimate phase distortion, pressure loss, focal displacement, skull heating, and off-target exposure. Phased-array systems can compensate for individual phase delays and electronically steer the acoustic focus. A 2025 study used a helmet-shaped array containing 256 independently controlled elements, individualized planning, stereotactic immobilization, and simultaneous functional MRI. The system selectively targeted the lateral geniculate nucleus and produced reproducible changes in connected visual cortical activity. This work provided proof that small human thalamic nuclei can be modulated noninvasively with high anatomical specificity [4, 7, 14]. Another 2025 investigation delivered ultrasound to the internal globus pallidus in patients with implanted deep-brain-stimulation electrodes. Direct local-field-potential recordings demonstrated frequency-dependent changes in pallidal oscillatory activity, with effects persisting after stimulation. These findings provide electrophysiological evidence that ultrasound can engage a predefined deep cerebral target rather than acting exclusively through superficial auditory or somatosensory pathways [8, 9, 25].

Clinical Applications. Parkinson's disease is a logical application because abnormal basal-ganglia oscillations provide measurable physiological targets. Pilot studies have examined repeated low-intensity stimulation of motor and basal-ganglia networks, with preliminary changes in bradykinesia, motor performance, and oscillatory activity. Direct pallidal recordings now strengthen the biological plausibility of noninvasive basal-ganglia neuromodulation. These findings should not be interpreted as evidence that ultrasound has replaced deep brain stimulation. Existing studies involve small cohorts, short follow-up, different protocols, and incompletely standardized clinical outcomes [10, 13, 23].

Drug-resistant epilepsy. Low-intensity ultrasound may suppress epileptogenic activity without tissue resection or electrode implantation. A pilot study performed in patients undergoing stereo-electroencephalographic monitoring directed ultrasound toward the seizure-onset zone. Intracranial recordings demonstrated local electrophysiological changes without MRI-visible destructive injury, although seizure responses were heterogeneous and one participant showed increased subclinical epileptic activity. The result illustrates both the potential and the risk of the method. Ultrasound is not intrinsically anticonvulsant; an inappropriate acoustic pattern may fail to inhibit or may potentially facilitate an unstable epileptic network. Randomized sham-controlled trials with prolonged seizure recording remain necessary [2, 3, 18].

Psychiatric disorders. Depression, anxiety, post-traumatic stress disorder, obsessive-compulsive disorder, and substance-use disorders are increasingly conceptualized as disturbances of distributed neural circuits. Focused ultrasound may permit reversible modulation of deep targets such as the amygdala, subcallosal cingulate region, anterior limb of the internal capsule, and striatal–limbic networks. Early studies have demonstrated target engagement and preliminary symptom changes, but many clinical investigations remain open-label or include small numbers of participants. Improvement may be influenced by placebo effects, regression to the mean, concurrent

treatment, and imperfect participant blinding. Therapeutic claims therefore require larger randomized studies [6, 13, 28].

Disorders of consciousness. The central thalamus participates in arousal, attention, and integration of cortical activity. Low-intensity ultrasound has been investigated as a method of stimulating thalamocortical networks in patients with prolonged disorders of consciousness following severe brain injury. Initial reports and subsequent mechanistic studies suggest that thalamic sonication may alter behavioral responsiveness, electrophysiological activity, or cerebral metabolism in selected patients. However, spontaneous fluctuation, diagnostic uncertainty, and the inability of many patients to report subjective adverse effects complicate interpretation. Ethical oversight and objective multimodal biomarkers are particularly important in this population [11, 12, 20].

Stroke, pain, and rehabilitation. Ultrasound is also being explored for post-stroke motor recovery and chronic pain. In rehabilitation, stimulation may enhance cortical excitability or plasticity when synchronized with task-specific training. In chronic pain, potential targets include the thalamus, insula, anterior cingulate cortex, and other components of nociceptive networks. At present, these applications remain experimental. Future studies must determine whether ultrasound produces clinically relevant improvement beyond intensive rehabilitation, medication, expectation, and repeated assessment [15, 17, 27].

Table 2. Current clinical-development areas

Clinical field	Principal proposed target	Current evidence level
Parkinson's disease	Motor cortex, globus pallidus, subthalamic and connected networks	Pilot and target-engagement studies
Drug-resistant epilepsy	Seizure-onset zone, hippocampus, thalamic nuclei	Early feasibility studies
Depression and anxiety	Amygdala, subcallosal cingulate, internal capsule	Small controlled and open-label studies
Disorders of consciousness	Central or related thalamic nuclei	Case reports and mechanistic trials
Chronic pain	Thalamic, insular, and cingulate networks	Early clinical investigation
Stroke rehabilitation	Motor cortex and connected sensorimotor networks	Feasibility and pilot trials
Cognitive neuroscience	Thalamic and cortical functional circuits	Experimental human studies

Safety and Methodological Challenges. Low-intensity stimulation is designed to avoid permanent tissue injury, but noninvasive delivery should not be equated with absence of risk. Potential adverse effects include headache, scalp discomfort, dizziness, nausea, fatigue, transient cognitive or mood changes, auditory sensations, unintended excitation, seizure aggravation, and off-target network modulation. Thermal and mechanical exposure must be evaluated separately. The skull may absorb energy and heat more than the targeted brain tissue. Acoustic modeling should therefore estimate scalp, skull, and intracranial exposure. Repeated sessions require cumulative-dose assessment rather than evaluation of a single sonication only. The ITRUSST consortium has published standardized reporting, practical-application, and biophysical-safety recommendations. These documents emphasize disclosure of the transducer and driving system, free-field measurements, pulse parameters, estimated intracranial exposure, thermal modeling, mechanical indices, targeting procedures, sham conditions, and adverse events [16, 23, 30]. Auditory confounding is a major methodological issue. Pulsed ultrasound can generate audible sensations through bone conduction. If participants recognize active stimulation, subjective clinical outcomes may be biased. Credible sham stimulation, acoustic masking, active-control targets, and post-session assessment of blinding are therefore required. Reproducibility is limited by inconsistent terminology and incomplete reporting. Two studies described as "low-intensity focused ultrasound" may deliver markedly different intracranial acoustic exposures. Standardization should not require that every

disease use an identical protocol, but it should permit accurate reconstruction and comparison of each protocol [21, 24, 31].

Discussion. Low-intensity transcranial focused ultrasound occupies an intermediate position between noninvasive cortical stimulation and implanted deep brain stimulation. It offers deeper and more focal targeting than conventional transcranial electrical stimulation while avoiding electrode implantation. The technology may serve several distinct roles. It can be used as a research instrument to test causal relationships between neural circuits and behavior. It may function as a reversible presurgical test of deep-brain targets. It may augment rehabilitation by promoting activity-dependent plasticity. Finally, repeated sonication may eventually become a therapeutic neuromodulation strategy [1, 10, 13, 32]. These applications require different evidentiary standards. Demonstrating transient target engagement in healthy participants does not prove therapeutic benefit in a chronic neurological disorder. Similarly, a short-term reduction in symptoms does not establish durability, disease modification, or superiority over existing treatment. Future trials should combine clinical outcomes with objective biomarkers such as intracranial electrophysiology, EEG, functional MRI, perfusion imaging, wearable measurements, or validated behavioral tasks. The acoustic protocol should be locked before validation, and models should be tested in centers not involved in their development. Personalization will probably be central to successful implementation. Treatment planning should incorporate skull characteristics, functional network organization, target geometry, disease phenotype, and individual physiological response. The same nominal device output cannot be assumed to deliver the same intracranial dose to every patient [23, 30, 32].

Conclusion. Low-intensity transcranial focused ultrasound is one of the most promising emerging technologies in noninvasive neuromodulation. It can reach cortical and deep brain structures with relatively high spatial precision and can produce immediate or persistent changes in neural activity without intentional tissue destruction. Early human investigations support target engagement in the thalamus, basal ganglia, hippocampus, amygdala, motor cortex, and distributed functional networks. Potential clinical applications include Parkinson's disease, drug-resistant epilepsy, depression, disorders of consciousness, chronic pain, and neurological rehabilitation. Nevertheless, the technology remains investigational. Current evidence is dominated by pilot studies, small cohorts, heterogeneous acoustic protocols, and limited follow-up. Routine clinical use cannot yet be recommended outside approved research protocols. Progress toward clinical implementation requires individualized acoustic modeling, standardized reporting, credible sham control, objective target-engagement biomarkers, detailed neuropsychological surveillance, and independent multicenter validation.

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