REVIEW

Focused Ultrasound for the Treatment of Circuit and Molecular Pathology in Parkinson's Disease

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ABSTRACT: Focused ultrasound is rapidly emerging as a novel technology for the development of symptomatic therapies and supporting disease-modifying treatments for Parkinson's disease (PD). At the forefront of this development is thermoablation using high-intensity focused ultrasound, an incisionless treatment that has been extensively tested in clinical trials and so far has received clinical approval for the treatment of essential tremor and PD patients. At the other end of the spectrum, low-intensity focused ultrasound has been demonstrated in both neuromodulation and blood–brain barrier opening to allow the entry of therapeutic molecules into the central nervous system. The aim of this review is both to provide an overview of the current and future roles of focused ultrasound in disease-modifying treatments for PD with a special focus on outlining the full complexity of the disease beyond dopaminergic cell loss and to bridge clinical and preclinical research. First, we establish PD as a disease including both circuit dysfunctions and molecular pathology. Second, we discuss focused ultrasound state-of-the-art clinically and when relevant in relation to other similar treatment strategies (ie, deep brain stimulation). Third, we highlight preclinical advances and the potential of focused ultrasound to become a disease-modifying treatment. Understanding the therapeutic effects of focused ultrasound in a complex disease like PD is necessary to harness the full potential of the technology. © 2026 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

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The disabling symptoms associated with Parkinson's disease (PD) include tremor, bradykinesia, and rigidity as cardinal motor features. The symptoms' association with degeneration of nigral dopaminergic neurons led to a focus on treatments aiming at increasing dopaminergic levels, for example, levodopa (L-dopa), or

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correcting for circuit dysfunctions induced by the loss of dopaminergic cells, for example, lesional therapies and deep brain stimulation (DBS).[1,2] However, PD also involves substantial molecular complexity. A major pathological hallmark of PD is accumulation of aggregated α-synuclein in neurons, and mutations or multiplications of the gene encoding α-synuclein, *SNCA*, result in familial forms of PD.[3-12] Whereas therapies targeting α-synuclein take up approximately 15% of clinical trials, other disease-modifying targets have emerged, such as inflammation, the lysosomal protein glucocerebrosidase, kinases including leucine-rich repeat kinase 2 (LRRK2), energy metabolism, and growth factors.[13] However, current approved medical and surgical paradigms still aim for symptom treatment, with some symptoms such as freezing of gait, dementia, psychiatric symptoms and rapid eye movement sleep disorder remaining difficult to treat.

Targeting both circuit and molecular pathologies, focused ultrasound has emerged as a novel technological framework to treat PD.[14] However, reviews have to a large extent treated clinical (focusing mainly on circuit dysfunctions) and preclinical (focusing on molecular treatments) advancements in the field separately. In this review, we introduce both aspects of the pathology and outline clinical and preclinical findings, including a discussion of the translatability of the preclinical findings. Our aim is to improve bench-to-bedside translation of focused ultrasound treatments, and also bedside-to-bench-driven research. We discuss focused ultrasound-based therapies for PD, which is divided into three categories: (1) high-intensity focused ultrasound (HIFU) for therapeutic lesioning with targeted local heating of the brain tissue; (2) low-intensity focused ultrasound modulation of brain cell activity through mechanoreceptors (transcranial ultrasound stimulation [TUS])[15-19]; (3) low-intensity focused ultrasound to increase the permeability of the blood–brain barrier (BBB, LIFU-B), through ultrasound-induced oscillation of an exogenous contrast agent resulting in a transient decrease in tight-junction proteins and efflux transporters and an increase in endothelial transcytosis (Fig. 1A).[20-25] Finally, we discuss future- and unexplored potentials of focused ultrasound for PD.

Pathology of PD: A Brief Review

Molecular Pathology of PD

The etiology of PD remains incompletely determined, and multiple starting points potentially exist, which ultimately cause the loss of neurons, particularly dopaminergic neurons. Presynaptic α-synuclein in healthy neurons can undergo reversible exchange between an unstructured cytoplasmic form and an α-helical vesicle-bound form, and α-synuclein aggregates can be transported along neuronal processes and exchanged between neurons.[26,27] Under the right conditions and posttranslational modifications, such as phosphorylation, ubiquitination, and truncation, α-synuclein aggregates into oligomers and fibrils, which can further develop into dense structures called Lewy bodies (LB).[28] Although it has been suggested that the extent of LB formation correlates with disease progression, this remains controversial, and LBs can be found postmortem in people without PD symptoms and are not present in all familial forms of PD.[29] Recently developed methods allow a highly sensitive detection of oligomeric α-synuclein aggregates in brain tissue, which could enable the investigation of the link between disease progression and oligomer formation.[30,31]

The role of α-synuclein in PD onset and progression remains to be determined, and PD is a multisystem disorder. The brain in patients exhibits decreased levels of autophagic and lysosomal markers, oxidative damage, mitochondrial dysfunctions, and signs of a chronic proinflammatory environment.[32-38] Cytokines are key modulators of the immune response, and the association of their activity with PD has led to phase 1 and 2 clinical trials, investigating interleukin-1β release and tumor necrosis factor α as targets for disease-modifying therapeutics,[13,39] NCT05924243 and NCT05962957. Genetic findings demonstrate that mutations in *SNCA* as well as in genes encoding glucocerebrocidase, LRRK2, and proteins important for mitochondrial function (DJ-1, Parkin, and phosphatase and tensin homologue-induced kinase 1) all cause familial forms of PD.[3-12,40-43] The accumulating dysfunctions eventually cause cell death, affecting multiple neuronal subtypes and circuits that are linked to different symptom developments in PD patients (reviewed in detail in McGregor and Nelson[44]). The dopaminergic, neuromelanin-containing neurons in substantia nigra pars compacta (SNc) are especially sensitive to PD pathology and are lost early in disease progression.[45] The increased sensitivity of this neuronal population is still not fully understood but has been suggested to be related to more extensive axonal branching and autonomous pacemaker activity.[45] In addition, dopamine, neuromelanin, and iron have been suggested to be functionally linked, and studies have found a correlation between dopaminergic dysfunctions and increased neuromelanin and iron deposits.[46]

A recent proposal suggests the segregation of PD patients based on the presence or absence of prodromal symptoms into "body first" or "brain first" pathologies, respectively.[47] Accumulation of phosphorylated α-synuclein in peripheral tissue can be found in early PD, and in some patients prodromal symptoms, for example, constipation, anosmia, and rapid eye movement sleep disorder, are seen prior to the onset of the classical motor symptom.[48,49] These markers and

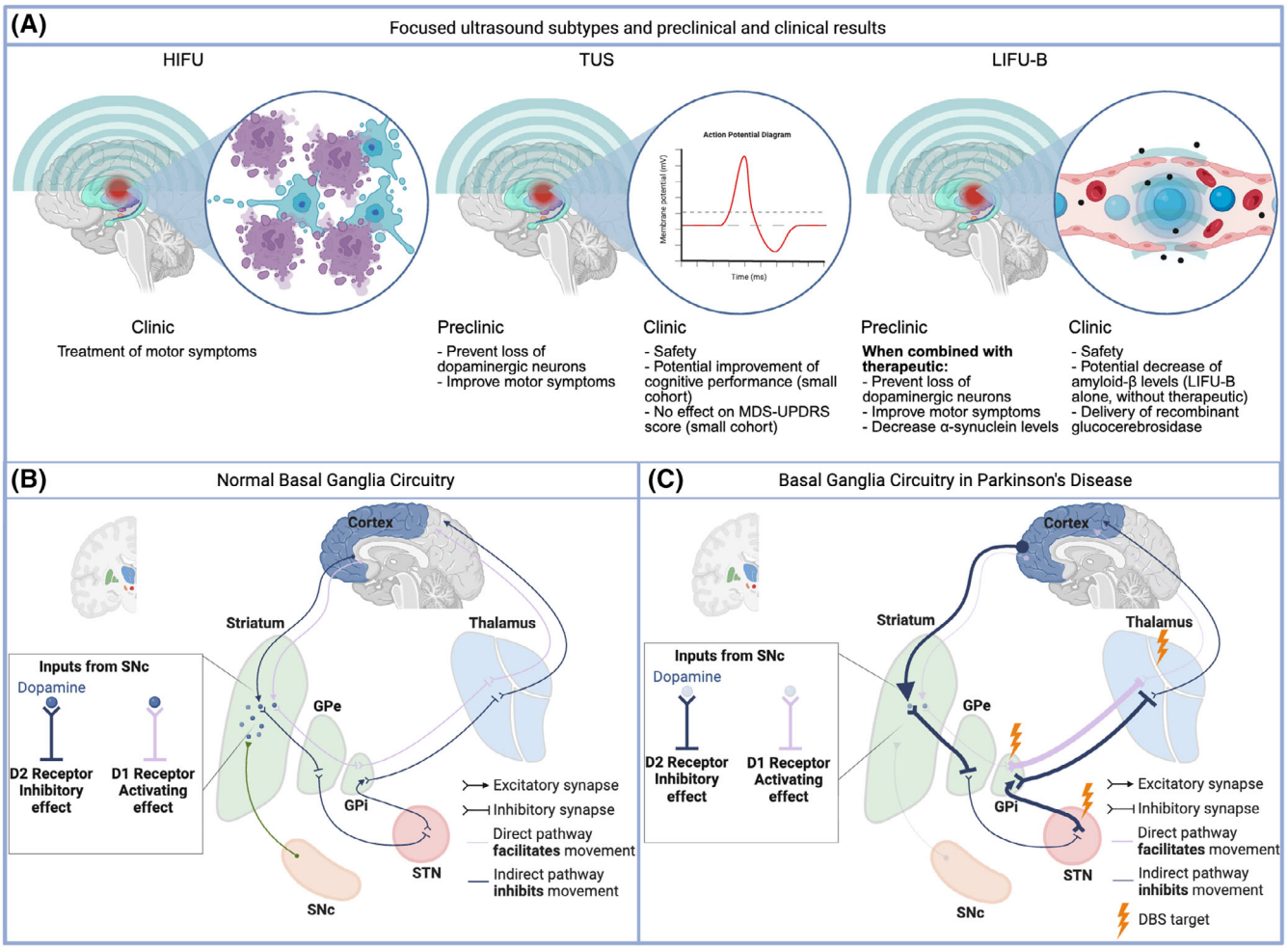

FIG. 1. Focused ultrasound subtypes and simplified model of normal and PD (Parkinson's disease)–related basal ganglia circuitry. (**A**) Focused ultrasound can be divided into high-intensity focused ultrasound (HIFU), transcranial ultrasound stimulation (TUS), and low-intensity focused ultrasound combined with bubbles (LIFU-B). HIFU is used in the clinic to treat tremor in PD patients, whereas TUS and LIFU-B primarily are investigated preclinically for the prevention of dopaminergic cell loss and motor dysfunctions. (**B**, **C**) Basal ganglia (BG) consist of the caudate and putamen, together called the dorsal striatum; the globus pallidus (GP), subdivided into pars interna (GPi) and pars externa (GPe); the subthalamic nucleus (STN); the nucleus accumbens; and the olfactory tubercle. Of some importance in relation to PD, the substantia nigra (SN), subdivided by its microscopic appearance in pars compacta (SNc) and pars reticulate (SNr), is included. It is important to note that the BG are involved in many aspects of brain function apart from movement, comparably modulated by dopamine, including limbic and cognitive functions. Subsequently, the affected motor circuits are thus used as an example of a more general degeneration and shift in circuit dynamics taking place within the BG. The caudate–putamen together make up the dorsal striatum, which serves as the primary input nuclei of the basal nuclei. Most cortical areas project to the striatum. The striatum consists almost entirely (95%) of medium spiny projection neurons. These form both the major input and output cells of the striatum. They are universally GABAergic, with variation in co-transmitters based on the location of the projection. Importantly, they differentially express either D1- or D2-type dopamine receptors, with a small subpopulation co-expressing D1 and D2 receptors. The final 5% of the neurons in the striatum are interneurons, mostly positive for acetylcholine. The output from the striatum, facilitated by the medium spiny projections, sends inhibitory output to both the GPe and GPi. The neurons projecting to the GPi contain GABA and substance-P, and are positive for dopamine D1 receptors. The GPe receives GABAergic/enkephalinergic neurons, positive for dopamine D2 receptors. The cortico-striatal-GPi pathway is known as the "direct" pathway, whereas the cortico-striatal-GPe pathway is known as the "indirect" pathway. As a corollary, the GPi and SN together form the output nuclei of the BG, as they are the structures that interface with nuclei and areas of the brain outside the BG. For the SN, the inputs are inhibitory projections from the GPe and excitatory from the STN. In addition, the SN projects to the thalamus, the superior colliculus and the peduncolopontine nucleus. Briefly, the activation of the direct pathway means a glutamatergic signal acts on the striatum, increasing GABAergic inhibition of the GPi. The GPi in turn ceases tonic inhibition of the thalamus, with the net result being increased motor cortical activity. On the contrary, activation of the indirect pathway entails glutamatergic activation of the striatum, increasing inhibitory signals to the GPe. This in turn disinhibits GABAergic inhibition of the GPi, thus resulting in increased tonic inhibition from the GPi to the thalamus, resulting in decreased propagation of motor signals. This scheme, although simple provides an intuitive understanding of the STN or GPi as targets of choice for modulatory treatments, has however been challenged by recent evidence, implying that the functional connectivity is more complicated than indicated here; created using BioRender.com. [Color figure can be viewed at wileyonlinelibrary.com]

symptoms can therefore offer early predictors for the initiation of treatment with therapeutics, for example, targeting α-synuclein progression or supporting neuronal health.

Pathological Circuitry in PD in Relation to Surgical Treatment

Normal Transmission through the Basal Ganglia. The striatum serves as the primary input

nuclei of the basal nuclei and receives projections from most cortical areas (Fig. 1B). Morphologically, the striatum consists almost entirely (95%) of medium spiny projection neurons. They are universally GABAergic with differentially expressed D1-type or D2-type dopamine receptors and a small subpopulation co-expressing both receptors. Facilitated by the medium spiny projections, the striatum sends inhibitory output to the external (GPe) and the internal (GPi) globus pallidus. The neurons projecting to the GPi and GPe are positive for dopamine D1 and D2 receptors, respectively. The cortico-striatal-GPi pathway is known as the "direct" pathway, whereas the cortico-striatal-GPe pathway is known as the "indirect" pathway. Activation of the direct pathway results in increased GABAergic inhibition of the GPi, which ceases tonic inhibition of the thalamus, with a net increased motor cortical activity. On the contrary, activation of the indirect pathway increases inhibitory signals to the GPe, hereby disinhibiting GABAergic inhibition of the GPi and resulting in decreased propagation of motor signals. In all this, the dopaminergic projections from the SN serve a modulatory role. This scheme provides an intuitive understanding of the subthalamic nucleus (STN) or GPi as neuromodulatory targets; however, recent evidence implies that functional connectivity is more complicated than indicated here.

Pathological Transmission in PD in Relation to Surgical Treatment. The pronounced loss of dopaminergic projection neurons in the SNc induced by PD-related molecular pathology causes the disruption of the modulatory function of dopamine (Fig. 1C). Dopaminergic deficiency results in decreased activity of the excitatory and D1-positive direct cortico-striatal pathway. Conversely, dopamine loss disinhibits the indirect, inhibitory, and D2-positive cortico-striatal pathway, resulting in an overall inhibition of output from the striatum. Taken together, deficiency of dopamine transmission causes loss of striatal excitation, which in turn causes disinhibition of GPi and STN. As these structures deliver inhibitory signals to the thalamus, the result is an overall decrease in the activity of thalamocortical transmission leading to akinesia and rigidity. This also serves to explain the prevalence of dyskinesia using extended L-dopa therapy. The association between circuit and molecular mechanisms shows evidence suggesting a sensitization of D1 and D2 receptors and an increasingly dysregulated presynaptic metabolism and clearance of dopamine with prolonged disease. This implies dopamine hypersensitivity, and exogenously applied dopamine results in an exacerbated D1 and D2 response and exaggerated striatal excitability, the end result of which is decreased action selectivity resulting in dyskinetic movements. Further, the loss of SN-dopaminergic activity affecting the STN can result in increased β-band activity, implying that thalamic inhibition from dopamine loss is oscillatory.[50,51]

Neuromodulatory Treatment of PD Circuit Dysfunctions Using DBS and HIFU

HIFU and DBS for Motor Symptoms of PD

The motor symptoms resulting from PD circuit dysfunctions can generally be managed by neuromodulatory treatments such as DBS and magnetic resonance–guided HIFU. The choice to offer either treatment depends not only on the expected clinical effect but also on the nature of individual symptoms, patient preference, and similar factors. Furthermore, DBS targets are mostly STN or GPi, and so far, HIFU is mostly described for the ventral intermediate nucleus (VIM) of the thalamus. This target stratification therefore confers slightly different symptomatic effects.

Evidence for the clinical utility of HIFU in PD is collated through a systematic search of the literature (Appendix S1).

HIFU leads to robust and lasting effects on tremor, although long-term data are still somewhat forthcoming. Changes in tremor-related outcome measures, such as the Clinical Rating Scale for Tremor and the tremor subsections of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Part III, are robust in all published cohorts 3 to 12 months after treatment (Fig. 2; Appendix S1). One study included a long-term assessment of up to 5 years and found complete relapse of tremor in 7.69% (2 patients) and partial relapse in 30.76% (8 patients) of the treated patients.[52] Additionally, differentiated effects depend on target. Across all reports, HIFU was able to alleviate tremor by 67.78% (95% confidence interval [CI]: 56.78%–78.77%).

Broadening the scope to motor symptoms in general and including all targets, HIFU is an effective symptomatic treatment showing an estimated improvement of 40.25% (95% CI: 35.92%, 44.55%), corresponding to 11.53 points on MDS-UPDRS, Part III, in the *on* medication state (95% CI: 9.07, 14.72) (Fig. 2B). Stratified by target improvements are GPi/pallidothalamic tractotomy (PTT): 43.65% (95% CI: 32.59, 54.70%), STN: 38.98% (95% CI: 32.92, 44.47%), and VIM: 44.51% (95% CI: 29.28, 59.73%).

This is comparable, although slightly lower than that indicated by the extensive literature for DBS (Supporting Information), showing 44.94% improvement (95% CI: 41.35%, 48.53%) in the *off* medication state (Fig. S1).[53-65] Thus, in cases where DBS may not be feasible, HIFU seems to offer a reasonable alternative. It is important to be clear that this conclusion can be drawn only regarding patients with tremor as the main symptom because most data from HIFU treatment have VIM as target, and STN for DBS. Additional

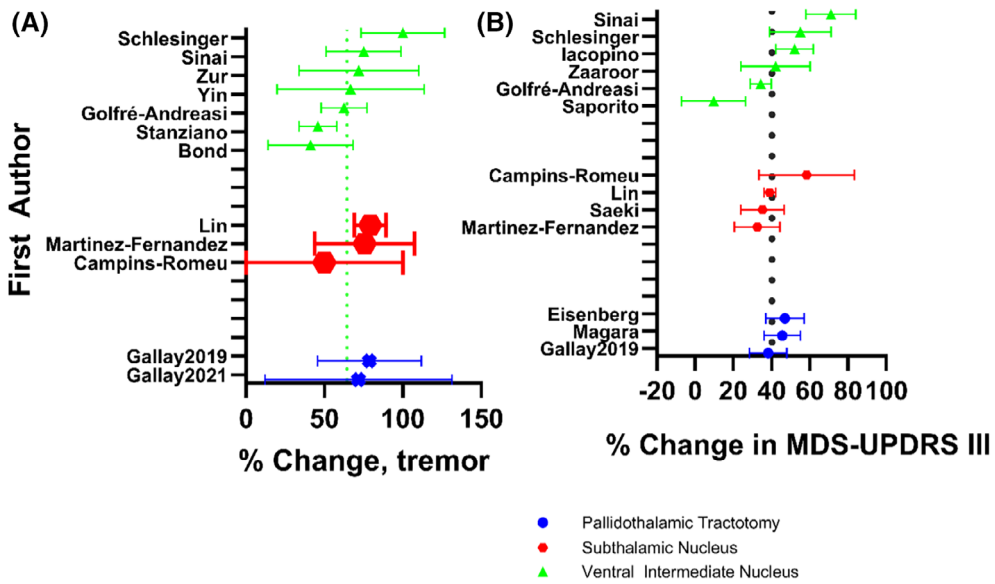

FIG. 2. Clinical effects of HIFU (high-intensity focused ultrasound) on PD (Parkinson's disease). (**A**) Forest plot of percentage change in tremor scales before and after HIFU stratified by target. Green line indicates mean improvement for VIM. PTT (pallidothalamic tractotomy), including GPi (internal globus pallidus) lesion, STN (subthalamic nucleus), and VIM (ventral intermediate nucleus of the thalamus). (**B**) Forest plot of the overall motor symptom effects of HIFU in different targets as reported by included studies. The black dashed line indicates the weighted mean motor symptom improvement. All points and attendant confidence intervals (CI) are given as percentage improvement in the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's disease Rating Scale, Part III, in the *on* medication state. For each target, the improvements are PTT: 43.65% (95% CI: 32.59, 54.70%), STN: 38.97% (95% CI: 33.23, 44.71%), and VIM: 44.51% (95% CI: 29.28, 59.73%). [Color figure can be viewed at wileyonlinelibrary.com]

sources of bias in the current literature include limited availability of longer-term investigations and several studies being conducted in an experimental setting, which may lead to an overestimation of effect sizes. Furthermore, true double blinding in the HIFU setting is generally not feasible, which could lead to an inflation of initial treatment effects.

Circuit- and Molecular-Level Corrections Using HIFU and DBS

Although HIFU has clear inhibitory effects on targeted circuit nodes, the overall, circuit-level alteration is less clear. Presumably, pallidotomies or subthalamotomies exert antiparkinsonian effects by disrupting the indirect pathway, either by removing the inhibitory effects of GPi on the thalamus or upstream by disrupting STN activation of the GPi.[66,67]

Interestingly, "temporary" thalamotomy from microlesioning during DBS electrode insertion can cause tremor reduction that relapses as perisurgical edema subsides.[68,69] Furthermore, STN-DBS causes local release of GABA from GPe, increasing the inhibitory activity on the STN and subsequent disinhibition of the thalamus.[70] Conversely, evidence indicates increased activation after DBS, including increased excitatory neurotransmitter release or increased blood flow.[71] Taken together, this entails a need to instead focus on the effects at the network level. This circuit-level view seems particularly compelling as there is no clear evidence of either DBS or thalamotomy-related effects on dopaminergic neuronal signaling,[72,73] with reports showing continuing progression of dopaminergic neuron loss[74] and only sparse and inconclusive evidence to the contrary.[75,76]

The Potential of Low-Intensity Focused Ultrasound for Neuromodulation and Disease-Modifying Treatments

HIFU has demonstrated therapeutic efficacy in clinical trials; however, it does not target the underlying molecular pathology of PD such as the proinflammatory environment, autophagic dysfunctions, oxidative damage, and α-synuclein aggregation. For targeting the progression of molecular pathology, low-intensity focused ultrasound has provided promising results in clinical trials and preclinical research.

Low-Intensity TUS

TUS can modulate the activity of neurons in the targeted areas and can be used to target highly diverse brain areas from cortical structures to deep-brain regions depending on the treatment goal, for example, to alleviate motoric or cognitive symptoms (Fig. 1A; Table S1). Similar to DBS, TUS is a reversible neuromodulatory treatment but with the ability to noninvasively target deep brain structures.[77] TUS can therefore easily be positioned to target multiple different brain regions in a single treatment as opposed to DBS that is limited to targeting the brain region where

the electrodes are inserted. TUS can activate receptors and induce both decreased and increased neuronal responses.[16-19] TUS stimulation in nonhuman primates simultaneous with behavior tasks improved motivation and decision accuracy, and repeated TUS treatments in preclinical animal models result in disease-modifying effects (Table 1).[78] It is not known whether TUS can induce long-term therapeutic effects in humans, and protocols to achieve this must be developed because clinical transducers are not currently wearable and suitable for sustained stimulation.

Clinical Trials. Opposed to HIFU, neuromodulation with TUS has not yet been investigated in sufficiently large cohorts of patients to demonstrate robust therapeutic effects. Five studies have applied TUS treatments in patients with PD and confirmed safety of the treatment.[77,87-90] Nicodemus et al showed TUS-induced cognitive improvement (timepoint for assessment not provided) in 27.3% of patients in a cohort, including 11 Alzheimer's disease (AD) and 11 PD patients; however, 13.6% exhibited a decline in cognition, demonstrating that the treatment had an effect only on a subgroup.[77] In addition, the choice of a 2-MHz frequency may have negatively influenced the ability of ultrasound to propagate through the skull.[91] The safety of TUS was recently confirmed by Hu et al in the largest study of TUS in PD patients so far, including 56 patients with PD and cognitive impairments randomly assigned between the TUS treatment group and the sham group.[89] The results demonstrated a significant improvement compared to baseline in Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) of 1.0 and 4.5 points, respectively, after sham treatment and 2.0 and 7.0 points, respectively, after TUS treatment. Similar to Nicodemus et al, the timepoint for these assessments is not provided. At the same time TUS improved MoCA and MMSE only with 2.0 points compared to sham.[89] The study demonstrates a large placebo effect on cognitive functions, which interestingly was also observed on serum neurotransmitter levels, warranting caution when interpretating positive treatment effects of TUS in studies where a proper sham treatment is not included. In addition, Grippe et al and Darmani et al enrolling 20 and 10 patients, respectively, showed target engagement through changes in cortical excitability within 60 min of the treatment, which depended on L-dopa dose.[88,90] In fact, Grippe et al observed only effects on cortical excitability and reduced bradykinesia induced by TUS in patients on medication.[88] Using these findings, the same group demonstrated in Samuel et al that

TABLE 1 *Overview of TUS treatments in animal models of PD*

TUS parameters	Target	Outcome measures	Animal model	References
3.8 MHz, 50% DC, 1 kHz PRF, 0.5 ms TBD, 4 s ISI, 1 s SD, 30 min/d	Subthalamic nucleus or globus pallidus	TH expression, markers of apoptosis, motor function	Mouse + MPTP	79
0.8 MHz, 760 mW/cm^2, 10% DC, 0.1 kHz PRF, 10 s ISI, 6 s SD, 40 min/d	Motor cortex	Motor function, antioxidant levels	Mouse + MPTP	80
0.5 MHz, 5100 mW/cm^2, 5% DC, 1 kHz PRF, 1 s ISI, 0.5 s SD, 0.39 MPa, 5 min/d	Subthalamic nucleus	Motor function	Mouse + MPTP	81
1 MHz, 100–300 mW/cm^2	No information	Dopamine release, TH expression, motor function	Mouse + MPTP	82
0.5 MHz, 2600 mW/cm^2, 1 kHz PRF, 0–5 ms TBD, 10 min/d	Unfocused	(FA) and relaxation time T2*	Rat + 6-OHDA	83
1 MHz, 123–110.667 mW/cm^2, 20% DC, 1 kHz PRF, 10 min/d	No information	TH expression, apoptosis, motor function	Mouse + MPTP	84
3.8 MHz, 430 mW/cm^2, 50% DC, 1 kHz PRF, 4 s ISI	Subthalamic nucleus	TH expression, inflammation, antioxidants, motor function	Mouse + MPTP + probenecid	85
1 MHz, 528 mW/cm^2, 5% DC, 1 kHz PRF, 50 ms TBD	Multiple brain regions	TH expression, GDNF, lidocalin 2 and interleukin 1β levels, motor function	Rat + 6-OHDA	86

Abbreviations: TUS, transcranial ultrasound stimulation; PD, Parkinson's disease; DC, duty cycle; PRF, pulse repetition frequency; TBD, tone burst duration; ISI, interstimulation interval; SD, sonication duration; TH, tyrosine hydroxylase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; FA, fractional anisotropy; 6-OHDA, 6-hydroxydopamine; GDNF, glial cell line–derived neurotrophic factor.

an accelerated TUS protocol could induce changes in cortical excitability measured immediately after sonication in 10 patients *off* medication.[87] The protocol also induced a trending decrease in upper-extremity rigidity assessed shortly after treatment, which was observed only in patients with a baseline score ≥3.[87] The field of TUS, in general, is currently working toward improving reproducibility where attention should be on patient selection, medication state depending on the chosen TUS protocol, and the implementation of proper sham controls.[92,93] This includes masking the auditory effects of TUS, as done by Grippe et al, as this can induce changes in TMS measurements.[94-96] In addition, when TUS is applied through the human skull, aberrations caused by the skull must be accounted for to ensure target specificity.[97] Indeed, it was recently demonstrated that sustainable decreases in tremors in essential tremor patients could be achieved for several minutes when applying TUS and accounting for skull aberrations.[98]

Preclinical Findings and Translation. TUS can induce neuronal activation in both superficial and deep brain structures. The therapeutic potential of this has been investigated in toxin-induced animal models of PD using different TUS parameters (Table 1). The toxins induced a primarily dopaminergic depletion of otherwise-healthy neurons through oxidative stress and mitochondrial dysfunction.[99,100] In these models, TUS has been used to stimulate several nodes of the cortico-basal ganglia-cortical circuit, including GP, STN, and motor cortex.[79,80] Although TUS is used to target similar circuits as HIFU, the outcomes in preclinical studies primarily focused on the molecular effects, including loss of tyrosine hydroxylase (TH)–positive cells in SNc, oxidative stress and apoptosis, and motor function.[79,80,83,84]

Preclinical TUS treatments of toxin-induced models typically result in a complete or partial inhibition of dopaminergic cell loss, which might explain most of the beneficial effects seen.[79,82,84,85] In the brains of PD patients, a substantial cell loss has already occured by the time of diagnosis. Although progress is observed in both fluid-based, peripheral tissue and imaging biomarkers, it remains challenging to identify PD patients prior to symptom onset (reviewed in detail elsewhere[101,102]), and TUS treatments cannot currently be initiated in time to prevent dopaminergic cell loss to the point of total restoration. Neuronal stimulation by DBS has demonstrated neuroprotective and disease modulatory effects in synucleinopathy animal models; however, this is not clearly seen when DBS is applied in PD patients, which might be attributed to the disease stage at which the treatment is initiated (Fig. 3A).[103,104] Similarly, potential disease modulatory effects of TUS on dopaminergic cell loss might be observed only when the treatment is applied early in disease progression (Fig. 3A). It remains to be determined whether TUS exerts neuroprotective effects in PD patients and animal models of synucleinopathy. Combination with other disease-modifying treatments, for example, targeting α-synuclein, inflammation, or energy metabolism, might be needed to maintain the cells in a stage where they can respond to the TUS treatment.

Low-Intensity Focused Ultrasound Combined with Micro- and Nanobubbles

Low-intensity focused ultrasound combined with bubbles (LIFU-B) is used to transiently increase the permeability of the BBB (Fig. 1A).[20] As opposed to HIFU, TUS, and DBS, LIFU-B was primarily developed as a brain delivery mechanism, though preclinical and clinical studies, especially in the field of AD, have demonstrated that LIFU-B also has interesting neuromodulatory effects. The bubbles are gas-filled lipid or polymer vesicles, in either micro- or nanoscale size, some of which have traditionally been used as ultrasound contrast agents (Definity, SonoVue, Optison).[106,107] Clinically, only microbubbles have been used so far, but nanobubbles may offer increased delivery of therapeutics.[108]

Clinical Trials. Based on several preclinical studies demonstrating LIFU-B-induced decreased levels of amyloid-β plaques, increased neurogenesis in the hippocampus, and improved cognitive function, the first neurodegenerative patient group treated with LIFU-B was AD patients.[109-112] Clinical trials in AD have progressed toward assessing therapeutic effects, whereas studies in PD patients are currently focusing on proof-of-concept studies of safety and efficacy, with 3 to 7 patients enrolled in each study (Table S1). The first two studies confirmed that LIFU-B could be safely applied in PD patients with dementia, which is associated with amyloid-β pathology.[20,21,113] Gasca-Salas et al did not find significant reductions in amyloid-β levels on positron emission tomography (PET) scans in 4 patients 3 to 4 weeks after LIFU-B treatment targeting cortical areas; however, Pineda-Pardo et al demonstrated a significant decrease in amyloid-β using PET scans in 7 patients when measured 3 months after LIFU-B treatments targeting the striatum.[20,21] Decreased amyloid-β level has also been demonstrated using PET 3 months after LIFU-B treatments in AD patients.[114] Collectively, the results from these clinical trials suggest that the ability of LIFU-B to decrease amyloid-β pathology may be translated to patients. A third study using LIFU-B as a treatment in PD patients focused on patients with heterozygous loss-of-function mutations in *GBA1* encoding the lysosomal enzyme glucocerebrosidase, which increases the risk of developing PD.[22] Meng et al utilized LIFU-B for the delivery of intravenously administered recombinant glucocerebrosidase to

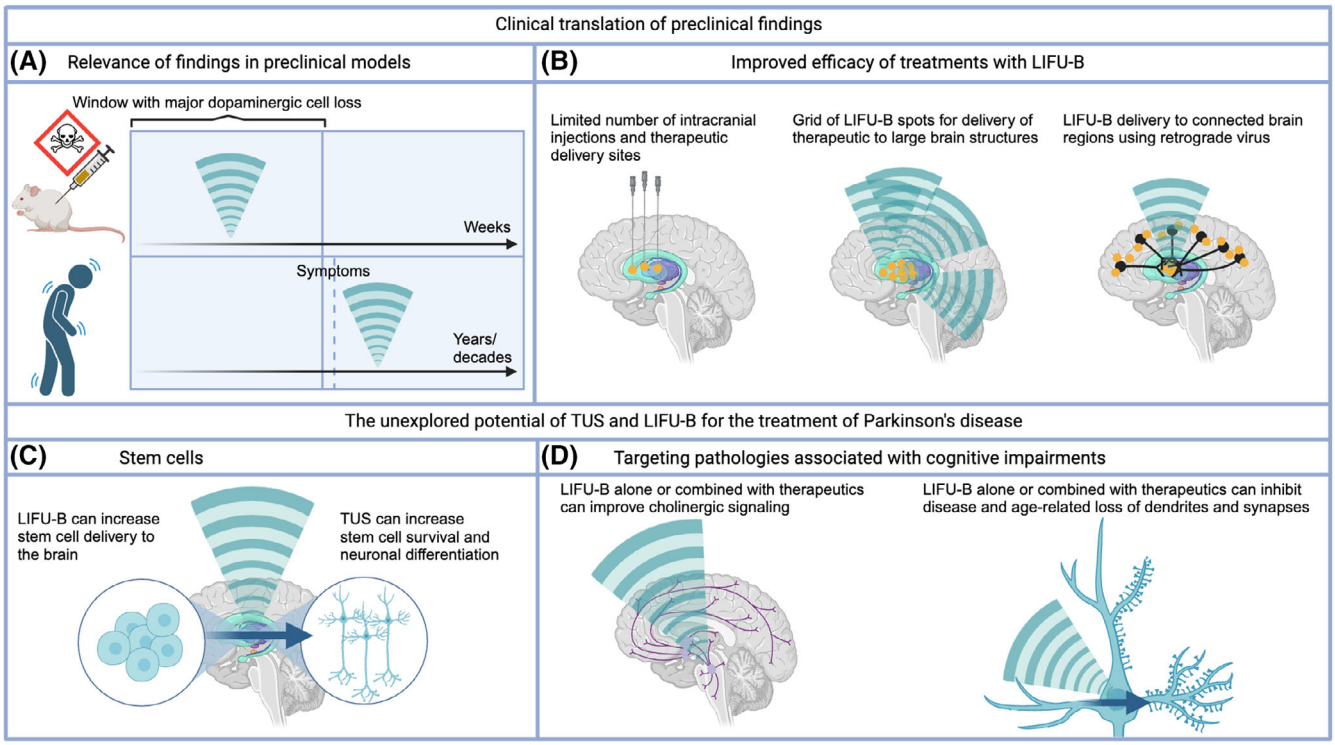

FIG. 3. Preclinical and clinical use and potential of focused ultrasound. (**A**) Preclinical findings show a substantial inhibition of dopaminergic cell loss after TUS (transcranial ultrasound stimulation) and LIFU-B (low-intensity focused ultrasound combined with bubbles) treatments; however, up to 90% dopaminergic cell loss observed at PD (Parkinson's disease) diagnosis hinders the opportunity to achieve similar effects in the clinic without predictive biomarkers.[105] (**B**) LIFU-B has the potential to improve the efficacy of treatments for PD by increasing the delivery of therapeutics to large or multiple brain regions. (**C**) TUS and LIFU-B can be combined with stem cells to increase stem cell delivery to the brain as well as survival and neuronal differentiation. (**D**) Cognitive symptoms in PD patients are associated with cholinergic dysfunctions and decreased levels of cortical synapses. LIFU-B has demonstrated the ability to improve both pathologies in animal models of AD (Alzheimer's disease) and normal aging, suggesting the use of LIFU-B to inhibit or slow the development of cognitive impairments in PD patients; created using BioRender.com. [Color figure can be viewed at wileyonlinelibrary.com]

the putamen and demonstrated a reduced metabolic rate in the targeted area 5 weeks after the last of three biweekly treatments, suggesting successful delivery and reduction in disease-associated hypermetabolism.[22,115] To date, LIFU-B has successfully been targeted to multiple regions in PD patients of relevance for therapeutic delivery, including the cortex, putamen (unilaterally and bilaterally), and the SNc.[20,21,116,117] Taken together, clinical trials support the safety of LIFU-B in PD patients.[116] This motivates the continued investigation of LIFU-B as a treatment of PD. As a delivery mechanism, the successful translation of LIFU-B as an approved treatment depends on choosing both the right target and the right therapeutic. As outlined later, preclinical studies have focused heavily on delivery of neuroprotective agents to areas with dopaminergic cell loss, whereas treatments targeting α-synuclein have been delivered more broadly to multiple brain areas.

Preclinical Findings and Translation. Utilizing LIFU-B for the opening of the BBB and delivery of therapeutics to the brain of PD animal models have been achieved using several different strategies, which are summarized in Table 2. In general, the therapeutics that have been investigated using LIFU-B in animal models of PD can be divided into recombinant proteins, small-molecule drugs, and DNA encoding RNA gene regulators or proteins.[118-121] The therapeutics have been delivered to the brain either by the application of LIFU-B after a direct intravenous injection of the therapeutic or by incorporation in or conjugation to a delivery vehicle from where they are released upon ultrasound stimulation (Table 2).[118,119,122]

The main focus of the preclinical studies using LIFU-B for the delivery of therapeutics to PD animal models is to inhibit the loss of dopaminergic cell bodies and projections and improve motor functions (Table 2). Similar to studies on TUS, the majority of the investigations of LIFU-B have focused on the effect in toxin-induced models. Only two studies, Xhima et al and Feng et al have used animal models of synucleinopathy enabling the assessment of the therapeutic effects of LIFU-B on α-synuclein levels and aggregates.[119,121] Xhima et al achieved 50% α-synuclein knockdown after LIFU-B-mediated delivery of an AAV encoding miRNA targeting α-synuclein mRNA in transgenic mice overexpressing wild-type human α-synuclein.[121]

TABLE 2 *Overview of LIFU-B treatments in animal models of PD*

Therapeutic	Delivery system	Outcome measures	Animal model	References
Intravenous administration				
Recombinant neurturin	None	Dopamine levels and TH expression	Mouse + MPTP	123
GDNF (DNA)	Conjugated to or incorporated in bubbles	GDNF, dopamine, GFAP and TUJ-1 levels, TH expression, motor function.	Rat + 6-OHDA	120
Nrf2 (DNA)	—	TH and DAT expression, ROS levels.	Rat + 6-OHDA	124
GDNF & BDNF (DNA)	—	Dopamine and caspase-3 levels, TUJ-1 expression, motor function.	Mouse + MPTP	125
Recombinant FGF20	—	FGF20, dopamine & metabolites levels, TH expression and TUNEL staining, motor function.	Rat + 6-OHDA	118
Curcumin	—	Curcumin levels and motor function.	Mouse + MPTP	122
Triptolide	—	Liver toxicity, α-syn, dopamine & metabolites levels, thioflavin staining, motor function.	Acute α-syn overexpression through viral injection	119
GDNF (DNA)	Incorporation in vehicles injected separate from bubbles	GDNF, dopamine, DOPAC, HVA levels, TH expression, motor function	Rat + 6-OHDA	126
Curcumin	—	Dopamine & metabolites levels, TH expression and motor function	Mouse+ MPTP	127
GDNF (DNA)	Incorporation in vehicle conjugated to bubbles	GDNF, dopamine, DOPAC levels, TH expression and motor function	Mouse + MPTP	128
GDNF (DNA)	—	Not possible to distinguish GDNF alone effects from GDNF combined with LIFU-B	Rat + 6-OHDA	129
GDNF & Nurr1 (DNA)	—	Not possible to distinguish GDNF&Nurr1 alone effects from GDNF&Nurr1 combined with LIFU-B	Rat + 6-OHDA	130
GDNF (DNA)	—	GDNF levels, TH expression and motor function	Mitopark mouse	131
GDNF (DNA)	AAV injected separate from bubbles	TH expression and motor function	Mouse + MPTP	123
miRNA (DNA)	—	α-syn expression	Transgenic mouse overexpressing α-syn	121
SIRT-3 (DNA)	AAV conjugated to bubbles	SIRT-3 expression	Rat (not PD model)	132

(Continues)

TABLE 2 *Continued*

Therapeutic	Delivery system	Outcome measures	Animal model	References
Intracranial administration				
Recombinant GDNF	Incorporation into bubbles	Not possible to distinguish effects from GDNF alone or when combined with LIFU-B	Rat + 6-OHDA	133
Intranasal administration				
Recombinant BDNF	Intranasal therapetics and intravenous bubbles	TH expression. Motor function test lacks BDNF only control.	Mouse + MPTP	134
Intraperitoneal administration				
Recombinant gastrodin	Intraperitoneal therapeutics and intravenous bubbles	Gastrodin, dopamine, Bcl-2, BDNF, PSD-95, and synaptophysin levels. TH and Caspase-3 expression	Mouse + MPTP	135

Abbreviations: LIFU-B, low-intensity focused ultrasound combined with bubbles; PD, Parkinson's disease; TH, tyrosine hydroxylase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; GDNF, glial cell line–derived neurotrophic factor; GFAP, glial fibrillary acidic protein; TUJ-1, neuron-specific class III β-tubulin; 6-OHDA, 6-hydroxydopamine; Nrf2, nuclear factor erythroid 2-related factor 2; DAT, dopamine transporter; ROS, reactive oxygen species; BDNF, brain-derived neurotrophic factor; FGF20, fibroblast growth factor 20; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; α-syn, α-synuclein; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; Nurr1, nuclear receptor related 1; mRNA, microRNA.

Similar levels of reduction can rescue dysfunctions in a mouse model with aggressive synucleinopathy and associated motor dysfunctions, suggesting that the LIFU-B-mediated delivery of miRNA resulted in a therapeutically relevant level of α-synuclein knockdown.[121,136] Feng et al delivered an anti-inflammatory compound, triptolide, to the brain in a mouse model of acute viral-mediated α-synuclein-induced pathology.[119] Delivery of triptolide to the brain significantly increased dopamine levels and motor function and decreased total α-synuclein levels, but the underlying mechanism is not described. Finally, one published conference abstract shows decreased α-synuclein levels after LIFU-B-mediated delivery of an anti-α-synuclein antibody compared to antibody treatment alone.[137] This confirms that antibodies delivered to the brain using LIFU-B can interact with intracellular targets, which is corroborated by similar findings using antibodies against the microtubule-associated protein, tau.[138] From a therapeutic perspective, the targeting of aggregated α-synuclein in affected brain regions or native α-synuclein in still-healthy regions using antibodies or gene therapies is particularly well suited for LIFU-B-mediated delivery as these biologics have very poor BBB penetrance.[139] In addition, α-synuclein aggregates are found in both the central and peripheral nervous systems.[48] There is therefore potential in combining some of the benefits of targeting both peripheral and central nervous system α-synuclein pathologies using intravenous delivery and LIFU-B, which cannot be achieved by either intravenous treatment or intracranial injections.

Besides the studies described earlier, LIFU-B-based treatments have been tested in multiple toxin-induced animal models and one transgenic model with mitochondrial dysfunction (Mitopark) (Table 2). Delivery of neuroprotective agents has been the main focus of LIFU-B application in toxin-induced models. Particularly trophic factors, including glial cell line–derived neurotrophic factor (GDNF), brain-derived neurotrophic factor, and neurturin, as well as the downstream protein nuclear receptor related 1 have received attention (Table 2). Outcome measures in toxin-induced models generally include the level of dopamine and metabolites, TH expression or number of TH-positive cells, and test of motor function. Seven studies have demonstrated significantly higher therapeutic effects on outcome measures when combining neuroprotective agents with LIFU-B-mediated delivery compared to when the neuroprotective agent or LIFU-B was used alone.[120,123,125,126,128,131,134] Other compounds demonstrating varying levels of therapeutic effects after LIFU-B delivery in toxin-induced models include fibroblast growth factor 20 and nuclear factor erythroid 2-related factor 2, and the chemical compounds curcumin and gastrodin.[118,122,124,127,135] Overall, LIFU-B enables the delivery of treatments in dosages high enough to overcome toxin-induced mitochondrial dysfunction and oxidative stress, but the lack of synucleinopathy and aging in these models warrants further investigation in other animal models, which exhibit more features of PD pathology.

GDNF and neurturin have so far failed to meet their primary endpoints in clinical trials.[140,141] However, postmortem analysis has demonstrated an increase in TH expression in areas treated with AAV-mediated transgenic neurturin expression.[142] The neurturin-positive area covered up to 12.4% of the putamen and 66.6% of the SN, which may not be enough to achieve a therapeutic effect of the treatment.[142] LIFU-B enables

gene delivery to large brain areas in the primate brain, such as the entire putamen, without associated needle track damage (Fig. 3B).[116] LIFU-B and novel gene vectors have the potential to improve the efficacy of treatments that have previously failed in clinical trials, which could increase their ability to reach a therapeutic effect in PD patients.

Future Perspectives of Focused Ultrasound for the Treatment of PDP

Treatment of Parkinsonian Symptoms Using HIFU

The present evidence shows a convincing effect of HIFU in PD. Targets have been derived from those of DBS (VIM, STN, GPi), all of which show a significant effect on motor symptoms on the treated side of the body compared to the control group.[143-145] There are currently only comparative studies between HIFU targets, and long-term results (>12 months) are available only for HIFU-subthalamotomy-treated patients.[146,147]

Several questions are currently in focus for the optimization of HIFU. First, the safety and efficacy of bilateral staged HIFU treatment and the optimal choice of the target and lesion shape for the respective PD subtypes must be determined to ensure personalized treatments with minimal side effects.[148-150] Previous ablation techniques and modulation methods suggest using STN as "broad-spectrum" motor improvement, GPi for antidyskinetic target, VIM/posterior subthalamic area for tremor focus, and pedunculopontine nucleus for more investigational treatment for freezing of gait.[151-153] HIFU is currently FDA (U.S. Food and Drug Administration) and CE approved for unilateral thalamotomy (VIM) and pallidotomy (GPi) in PD as well as CE approved for unilateral targeting of STN and FDA approved for bilateral staged PTT (fibers from GPi to thalamus).

Second, the optimal timing, and target specification, of HIFU treatment during the course of the disease is not yet clear. HIFU treatment at an early stage of the disease could have a favorable influence on the course of the disease and reduce the symptom burden.[154] On the contrary, it is not clear at what age patients no longer benefit from HIFU treatment, as side effects such as gait instability can be difficult to treat.

Third, in addition to the aforementioned questions, direct comparisons with other device-based forms of therapy, such as DBS and medication pumps, are missing.

To summarize, HIFU treatment of PD is an effective and usually well-tolerated treatment option. The answers to the open questions will provide the basis for a more detailed assessment of the value of the therapy.

Stem Cells and TUS and LIFU-B

Recent breakthroughs in the use of stem cell transplantation have introduced the hope that lost dopaminergic neurons can be replenished in PD patients, at least to some degree[155,156] (NCT05635409). Several studies have provided results suggesting that TUS can increase the therapeutic efficacy of transplanted stem cells by increasing the survival and neuronal differentiation of the engrafted cells (Fig. 3C).[157-159] In addition, LIFU-B has been demonstrated to enable noninvasive delivery of intravenous stem cells to targeted brain areas (Fig. 3C).[160-164] TUS and LIFU-B thus have the potential to further increase the efficacy of the already-promising stem cell–based treatments for PD.

Targeting Cognitive Dysfunctions

Mild cognitive deficits are observed in at least 20% of PD patients at the time of diagnosis, and after 10 years almost half progress to dementia.[113] Studies using LIFU-B in models of AD have shown promising results for the targeting of dysfunctions in the cholinergic system, which is also highly affected in individuals with PD and dementia.[165-168] In addition, LIFU-B treatments alone can prevent age-related loss of dendrites in healthy mice, and increase pre- and postsynaptic markers in a toxin-induced PD mouse model.[135,169] The underlying mechanism behind LIFU-B-induced neuroplasticity is unknown but might be caused by an increase in trophic factors and the activation of microglia, which is highly involved in synaptic maintenance and pruning.[110,166,168,170] The aforementioned findings suggest that LIFU-B might be able to hinder or slow neuropathological changes associated with the development of dementia if the treatment is initiated shortly after the diagnosis of PD (Fig. 3D).

Conclusion

PD is a multisystem disorder acting at several organizational levels of the central nervous system. HIFU has demonstrated convincing therapeutic effects to target different parkinsonian symptoms. The safety of TUS and LIFU-B application in PD patients has been demonstrated, but FDA or CE approvals of low-intensity focused ultrasound treatments for PD have not yet been obtained. Clinical translation of preclinical findings using low-intensity focused ultrasound depends on further investigation with an increased focus on the relevance of the animal model and the findings for translation. In addition, venturing into yet unexplored potentials of focused ultrasound for the treatment of PD may lead to the development of novel therapies for dopaminergic replenishing and targeting of nonmotor symptoms of PD. ■

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R.H.K.: 1A, 1B, 1C, 3A, 3B.
V.S.H.: 1A, 1B, 1C, 2A, 2B, 3A, 3B.
J.A.P.P.: 3B.
J.B.: 3B.
S.P.: 3A, 3B.
A.T.: 3A, 3B.
J.J.: 3B.
A.N.G.: 1A, 2C, 3A, 3B.

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Data Availability Statement

Data is available from authors upon reasonable request.

References

1. Cooper IS. The Neurosurgical Alleviation of Parkinsonism. Springf., Ill: Charles C. Thomas; 1956.
2. Limousin-Dowsey P, Pollak P, Van Blercom N, Krack P, Benazzouz A, Benabid A. Thalamic, subthalamic nucleus and internal pallidum stimulation in Parkinson's disease. J Neurol 1999; 246(Suppl 2):II42–II45. https://doi.org/10.1007/BF03161080
3. Spillantini MG, Schmidt ML, Lee VMY, Trojanowski JQ, Jakes R, Goedert M. α-Synuclein in Lewy bodies. Nature 1997;388: 839–840.
4. Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the α-synuclein gene identified in families with Parkinson's disease. Science (New York, NY) 1997;276:2045–2047.
5. Krüger R, Kuhn W, Müller T, et al. AlaSOPro mutation in the gene encoding α-synuclein in Parkinson's disease. Nat Genet 1998;18(3): 106–108. https://doi.org/10.1038/ng0298-106
6. Zarranz JJ, Alegre J, Gómez-Esteban JC, et al. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol 2004;55(2):164–173. https://doi.org/10.1002/ana.10795
7. Appel-Cresswell S, Vilarino-Guell C, Encarnacion M, et al. Alpha-synuclein p.H50Q, a novel pathogenic mutation for Parkinson's disease. Mov Disord 2013;28(6):811–813. https://doi.org/10.1002/mds.25421
8. Kiely AP, Asi YT, Kara E, et al. A-Synucleinopathy associated with G51D SNCA mutation: a link between Parkinson's disease and multiple system atrophy? Acta Neuropathol 2013;125(5):753–769. https://doi.org/10.1007/s00401-013-1096-7
9. Pasanen P, Myllykangas L, Siitonen M, et al. A novel α-synuclein mutation A53E associated with atypical multiple system atrophy and Parkinson's disease-type pathology. Neurobiol Aging 2014; 35(9):2180.e1–2180.e5. https://doi.org/10.1016/j.neurobiolaging.2014.03.024
10. Yoshino H, Hirano M, Stoessl AJ, et al. Homozygous alpha-synuclein p.A53V in familial Parkinson's disease. Neurobiol Aging 2017;57:248.e7–248.e12. https://doi.org/10.1016/j.neurobiolaging.2017.05.022
11. Chartier-Harlin MC, Kachergus J, Roumier C, et al. α-Synuclein locus duplication as a cause of familial Parkinson's disease. Lancet 2004;364(9440):1167–1169.
12. Farrer M, Kachergus J, Forno L, et al. Comparison of kindreds with parkinsonism and α-synuclein genomic multiplications. Ann Neurol 2004;55(2):174–179. https://doi.org/10.1002/ana.10846
13. McFarthing K, Buff S, Rafaloff G, et al. Parkinson's disease drug therapies in the clinical trial pipeline: 2024 update. J Parkinsons Dis 2024;14(5):899–912. https://doi.org/10.3233/JPD-240272
14. Foffani G, Trigo-Damas I, Pineda-Pardo JA, Blesa J, Rodríguez-Rojas R, Martínez-Fernández R, Obeso JA. Focused ultrasound in Parkinson's disease: a twofold path toward disease modification. Mov Disord 2019;34(9):1262–1273. https://doi.org/10.1002/mds.27805
15. Meng Y, Hynynen K, Lipsman N. Applications of focused ultrasound in the brain: from thermoablation to drug delivery. Nat Rev Neurol 2021;17(1):7–22. https://doi.org/10.1038/s41582-020-00418-z
16. Oh SJ, Lee JM, Kim HB, et al. Ultrasonic neuromodulation via astrocytic TRPA1. Curr Biol 2019;29(20):3386–3401.e8. https://doi.org/10.1016/j.cub.2019.08.021
17. Yoo S, Mittelstein DR, Hurt RC, Lacroix J, Shapiro MG. Focused ultrasound excites cortical neurons via mechanosensitive calcium accumulation and ion channel amplification. Nat Commun 2022; 13(1):493. https://doi.org/10.1038/s41467-022-28040-1
18. Yoo SS, Bystritsky A, Lee JH, et al. Focused ultrasound modulates region-specific brain activity. Neuroimage 2011;56(3):1267–1275. https://doi.org/10.1016/j.neuroimage.2011.02.058
19. Min BK, Bystritsky A, Jung KI, et al. Focused ultrasound-mediated suppression of chemically-induced acute epileptic EEG activity. BMC Neurosci 2011;12:23. https://doi.org/10.1186/1471-2202-12-23
20. Gasca-Salas C, Fernández-Rodríguez B, Pineda-Pardo JA, et al. Blood-brain barrier opening with focused ultrasound in Parkinson's disease dementia. Nat Commun 2021;12(1):779. https://doi.org/10.1038/s41467-021-21022-9
21. Pineda-Pardo JA, Gasca-Salas C, Fernández-Rodríguez B, et al. Striatal blood–brain barrier opening in Parkinson's disease dementia: a pilot exploratory study. Mov Disord 2022;37(10):2057–2065. https://doi.org/10.1002/mds.29134
22. Meng Y, Pople CB, Huang Y, et al. Putaminal recombinant glucocerebrosidase delivery with magnetic resonance–guided focused ultrasound in Parkinson's disease: a phase I study. Mov Disord 2022;37(10):2134–2139. https://doi.org/10.1002/mds.29190
23. Sheikov N, McDannold N, Sharma S, Hynynen K. Effect of focused ultrasound applied with an ultrasound contrast agent on the tight junctional integrity of the brain microvascular endothelium. Ultrasound Med Biol 2008;34(7):1093–1104. https://doi.org/10.1016/j.ultrasmedbio.2007.12.015
24. Sheikov N, McDannold N, Jolesz F, Zhang YZ, Tam K, Hynynen K. Brain arterioles show more active vesicular transport of blood-borne tracer molecules than capillaries and venules after focused ultrasound-evoked opening of the blood-brain barrier. Ultrasound Med Biol 2006;32(9):1399–1409. https://doi.org/10.1016/j.ultrasmedbio.2006.05.015
25. Cho HS, Lee HY, Han M, et al. Localized Down-regulation of P-glycoprotein by focused ultrasound and microbubbles induced blood-brain barrier disruption in rat brain. Sci Rep 2016;6:1–10. https://doi.org/10.1038/srep31201
26. Burré J, Sharma M, Südhof TC. Cell biology and pathophysiology of α-synuclein. Cold Spring Harb Perspect Med 2018;8(3): a024091. https://doi.org/10.1101/cshperspect.a024091
27. Visanji NP, Brotchie JM, Kalia LV, Koprich JB, Tandon A, Watts JC, Lang AE. α-Synuclein-based animal models of Parkinson's disease: challenges and opportunities in a new era. Trends Neurosci 2016;39(11):750–762. https://doi.org/10.1016/j.tins.2016.09.003
28. Mahul-Mellier AL, Burtscher J, Maharjan N, et al. The process of Lewy body formation, rather than simply α-synuclein fibrillization, is one of the major drivers of neurodegeneration. Proc Natl Acad

Sci U S A 2020;117(9):4971–4982. https://doi.org/10.1073/pnas.1913904117

29. Koeglsperger T, Rumpf SL, Schließer P, et al. Neuropathology of incidental Lewy body & prodromal Parkinson's disease. Mol Neurodegener 2023;18(1):32. https://doi.org/10.1186/s13024-023-00622-7
30. Jensen NM, Vitic Z, Antorini MR, Viftrup TB, Parkkinen L, Jensen PH. Abundant non-inclusion α-synuclein pathology in Lewy body-negative LRRK2-mutant cases. Acta Neuropathol 2025;149(1):41. https://doi.org/10.1007/s00401-025-02871-w
31. Jensen NM, Fu Y, Betzer C, et al. MJF-14 proximity ligation assay detects early non-inclusion alpha-synuclein pathology with enhanced specificity and sensitivity. NPJ Parkinsons Dis 2024;10(1):227. https://doi.org/10.1038/s41531-024-00841-9
32. Chu Y, Dodiya H, Aebischer P, Olanow CW, Kordower JH. Alterations in lysosomal and proteasomal markers in Parkinson's disease: relationship to alpha-synuclein inclusions. Neurobiol Dis 2009;35(3):385–398. https://doi.org/10.1016/j.nbd.2009.05.023
33. Keeney PM, Xie J, Capaldi RA, Bennett JP. Parkinson's disease brain mitochondrial complex I has oxidatively damaged subunits and is functionally impaired and misassembled. J Neurosci 2006;26(19):5256–5264. https://doi.org/10.1523/JNEUROSCI.0984-06.2006
34. Imamura K, Hishikawa N, Sawada M, Nagatsu T, Yoshida M, Hashizume Y. Distribution of major histocompatibility complex class II-positive microglia and cytokine profile of Parkinson's disease brains. Acta Neuropathol 2003;106(6):518–526. https://doi.org/10.1007/s00401-003-0766-2
35. Gerhard A, Pavese N, Hotton G, et al. In vivo imaging of microglial activation with [11C](R)-PK11195 PET in idiopathic Parkinson's disease. Neurobiol Dis 2006;21(2):404–412. https://doi.org/10.1016/j.nbd.2005.08.002
36. McGeer PL, Itagaki S, Boyes BE, McGeer EG. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. Neurology 1988;38(8):1285–1291. https://doi.org/10.1212/wnl.38.8.1285
37. Mogi M, Harada M, Kondo T, Riederer P, Inagaki H, Minami M, Nagatsu T. Interleukin-1 beta, interleukin-6, epidermal growth factor and transforming growth factor-alpha are elevated in the brain from parkinsonian patients. Neurosci Lett 1994;180(2):147–150. https://doi.org/10.1016/0304-3940(94)90508-8
38. Liscovitch N, French L. Differential Co-expression between α-synuclein and IFN-γ signaling genes across development and in Parkinson's disease. PLoS One 2014;9(12):e115029. https://doi.org/10.1371/journal.pone.0115029
39. Dzamko N. Cytokine activity in Parkinson's disease. Neuronal Signal 2023;7(4):NS20220063. https://doi.org/10.1042/NS20220063
40. Hou X, Watzlawik JO, Fiesel FC, Springer W. Autophagy in Parkinson's disease. J Mol Biol 2020;432(8):2651–2672. https://doi.org/10.1016/j.jmb.2020.01.037
41. Tansey MG, Wallings RL, Houser MC, Herrick MK, Keating CE, Joers V. Inflammation and immune dysfunction in Parkinson disease. Nat Rev Immunol 2022;22(11):657–673. https://doi.org/10.1038/s41577-022-00684-6
42. Bose A, Beal MF. Mitochondrial dysfunction in Parkinson's disease. J Neurochem 2016;139:216–231. https://doi.org/10.1111/jnc.13731
43. Smeyne RJ, Noyce AJ, Byrne M, Savica R, Marras C. Infection and risk of Parkinson's disease. J Parkinsons Dis 2021;11(1):31–43. https://doi.org/10.3233/JPD-202279
44. McGregor MM, Nelson AB. Circuit mechanisms of Parkinson's disease. Neuron 2019;101(6):1042–1056. https://doi.org/10.1016/j.neuron.2019.03.004
45. Surmeier DJ, Obeso JA, Halliday GM. Selective neuronal vulnerability in Parkinson disease. Nat Rev Neurosci 2017;18(2):101–113. https://doi.org/10.1038/nrn.2016.178
46. Biondetti E, Santin MD, Valabrègue R, et al. The spatiotemporal changes in dopamine, neuromelanin and iron characterizing Parkinson's disease. Brain 2021;144(10):3114–3125. https://doi.org/10.1093/brain/awab191
47. Borghammer P. The brain-first vs. body-first model of Parkinson's disease with comparison to alternative models. J Neural Transm (Vienna) 2023;130(6):737–753. https://doi.org/10.1007/s00702-023-02633-6
48. Berg D, Borghammer P, Fereshtehnejad SM, Heinzel S, Horsager J, Schaeffer E, Postuma RB. Prodromal Parkinson disease subtypes - key to understanding heterogeneity. Nat Rev Neurol 2021;17(6):349–361. https://doi.org/10.1038/s41582-021-00486-9
49. Donadio V, Incensi A, Rizzo G, et al. Skin intraneural phosphorylated α-synuclein is a highly specific biomarker for early Parkinson's disease. Brain. Published online September 8 2025;awaf313. https://doi.org/10.1093/brain/awaf313
50. Wiest C, Tinkhauser G, Pogosyan A, et al. Local field potential activity dynamics in response to deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Neurobiol Dis 2020;143:105019. https://doi.org/10.1016/j.nbd.2020.105019
51. Wiest C, Tinkhauser G, Pogosyan A, et al. Subthalamic deep brain stimulation induces finely-tuned gamma oscillations in the absence of levodopa. Neurobiol Dis 2021;152:105287. https://doi.org/10.1016/j.nbd.2021.105287
52. Sinai A, Nassar M, Sprecher E, Constantinescu M, Zaaroor M, Schlesinger I. Focused ultrasound thalamotomy in tremor dominant Parkinson's disease: Long-term results. J Parkinsons Dis 2022;12(1):199–206. https://doi.org/10.3233/jpd-212810
53. Sharma VD, Patel M, Miocinovic S. Surgical treatment of Parkinson's disease: devices and lesion approaches. Neurotherapeutics 2020;17(4):1525–1538. https://doi.org/10.1007/s13311-020-00939-x
54. Schlesinger I, Sinai A, Zaaroor M. MRI-guided focused ultrasound in Parkinson's disease: a review. Parkinsons Dis 2017;2017:8124624. https://doi.org/10.1155/2017/8124624
55. Reddy A, Hosseini MR, Patel A, Sharaf R, Reddy V, Tabarestani A, Lucke-Wold B. Deep brain stimulation, lesioning, focused ultrasound: update on utility. AIMS Neurosci 2023;10(2):87–108. https://doi.org/10.3934/Neuroscience.2023007
56. Pooja NA, Pahuja SK, Veer K. Significance of MRI guided focused ultrasound thalamotomy for Parkinson's disease: a review. Curr Med Imaging 2021;17(6):714–719. https://doi.org/10.2174/1573405616666201223142505
57. Moosa S, Martínez-Fernández R, Elias WJ, Del Alamo M, Eisenberg HM, Fishman PS. The role of high-intensity focused ultrasound as a symptomatic treatment for Parkinson's disease. Mov Disord 2019;34(9):1243–1251. https://doi.org/10.1002/mds.27779
58. Lin F, Wu D, Yu J, et al. Comparison of efficacy of deep brain stimulation and focused ultrasound in parkinsonian tremor: a systematic review and network meta-analysis. J Neurol Neurosurg Psychiatry 2021;92(4):434–443. https://doi.org/10.1136/jnnp-2020-323656
59. Lee KS, Clennell B, Steward TGJ, Gialeli A, Cordero-Llana O, Whitcomb DJ. Focused ultrasound stimulation as a Neuromodulatory tool for Parkinson's disease: a scoping review. Brain Sci 2022;12(2):289. https://doi.org/10.3390/brainsci12020289
60. Krishna V, Sammartino F, Rezai A. A review of the current therapies, challenges, and future directions of transcranial focused ultrasound technology: advances in diagnosis and treatment. JAMA Neurol 2018;75(2):246–254. https://doi.org/10.1001/jamaneurol.2017.3129
61. Ko TH, Lee YH, Chan L, Tsai KWK, Hong CT, Lo WL. Magnetic resonance–guided focused ultrasound surgery for Parkinson's disease: a mini-review and comparison between deep brain stimulation. Parkinsonism Relat Disord 2023;111:105431. https://doi.org/10.1016/j.parkreldis.2023.105431
62. Fernandez-Garcia C, Alonso-Frech F, Monje MHG, Matias-Guiu J. Role of deep brain stimulation therapy in the magnetic resonance-guided high-frequency focused ultrasound era: current situation and future prospects. Expert Rev Neurother 2020;20(1):7–21. https://doi.org/10.1080/14737175.2020.1677465
63. Dallapiazza R, McKisic MS, Shah B, Elias WJ. Neuromodulation for movement disorders. Neurosurg Clin N Am 2014;25(1):47–58. https://doi.org/10.1016/j.nec.2013.08.002

64. Binder DK, Shah BB, Elias WJ. Focused ultrasound and other lesioning in the treatment of tremor. J Neurol Sci 2022;435:120193. https://doi.org/10.1016/j.jns.2022.120193

65. Metman LV, Slavin KV. Advances in functional neurosurgery for Parkinson's disease. Mov Disord 2015;30(11):1461–1470. https://doi.org/10.1002/mds.26338

66. Blond S, Caparros-Lefebvre D, Parker F, Assaker R, Petit H, Guieu JD, Christiaens JL. Control of tremor and involuntary movement disorders by chronic stereotactic stimulation of the ventral intermediate thalamic nucleus. J Neurosurg 1992;77(1):62–68. https://doi.org/10.3171/jns.1992.77.1.0062

67. Schuurman PR, Bosch DA, Merkus MP, Speelman JD. Long-term follow-up of thalamic stimulation versus thalamotomy for tremor suppression. Mov Disord 2008;23(8):1146–1153. https://doi.org/10.1002/mds.22059

68. Welter ML, Houeto JL, Bonnet AM, et al. Effects of high-frequency stimulation on subthalamic neuronal activity in parkinsonian patients. Arch Neurol 2004;61(1):89–96. https://doi.org/10.1001/archneur.61.1.89

69. Dostrovsky JO, Lozano AM. Mechanisms of deep brain stimulation. Mov Disord 2002;17(Suppl 3):S63–S68. https://doi.org/10.1002/mds.10143

70. Obeso JA, Marin C, Rodriguez-Oroz C, et al. The basal ganglia in Parkinson's disease: current concepts and unexplained observations. Ann Neurol 2008;64(Suppl 2):S30–S46. https://doi.org/10.1002/ana.21481

71. de Hemptinne C, Ryapolova-Webb ES, Air EL, et al. Exaggerated phase-amplitude coupling in the primary motor cortex in Parkinson disease. Proc Natl Acad Sci U S A 2013;110(12):4780–4785. https://doi.org/10.1073/pnas.1214546110

72. Löser J, Luthardt J, Rullmann M, et al. Striatal dopamine transporter availability and individual clinical course within the 1-year follow-up of deep brain stimulation of the subthalamic nucleus in patients with Parkinson's disease. J Neurosurg 2021;135:1–7. https://doi.org/10.3171/2020.8.JNS192740

73. Lokkegaard A, Werdelin LM, Regeur L, et al. Dopamine transporter imaging and the effects of deep brain stimulation in patients with Parkinson's disease. Eur J Nucl Med Mol Imaging 2007;34(4):508–516. https://doi.org/10.1007/s00259-006-0257-5

74. Hilker R, Portman AT, Voges J, et al. Disease progression continues in patients with advanced Parkinson's disease and effective subthalamic nucleus stimulation. J Neurol Neurosurg Psychiatry 2005;76(9):1217–1221. https://doi.org/10.1136/jnnp.2004.057893

75. Farokhniaee A, Lowery MM. Cortical network effects of subthalamic deep brain stimulation in a thalamo-cortical microcircuit model. J Neural Eng 2021;18(5):056006.https://doi.org/10.1088/1741-2552/abee50

76. Hesse S, Strecker K, Winkler D, et al. Effects of subthalamic nucleus stimulation on striatal dopaminergic transmission in patients with Parkinson's disease within one-year follow-up. J Neurol 2008;255(7):1059–1066. https://doi.org/10.1007/s00415-008-0849-z

77. Nicodemus NE, Becerra S, Kuhn TP, et al. Focused transcranial ultrasound for treatment of neurodegenerative dementia. Alzheimer's Dementia: Transl Res Clin Interventions 2019;5:374–381. https://doi.org/10.1016/j.trci.2019.06.007

78. Munoz F, Meaney A, Gross A, et al. Long term study of motivational and cognitive effects of low-intensity focused ultrasound neuromodulation in the dorsal striatum of nonhuman primates. Brain Stimul 2022;15(2):360–372. https://doi.org/10.1016/j.brs.2022.01.014

79. Zhou H, Niu L, Meng L, et al. Noninvasive ultrasound deep brain stimulation for the treatment of Parkinson's disease model mouse. Research 2019;2019:1–13. https://doi.org/10.34133/2019/1748489

80. Zhou H, Niu L, Xia X, et al. Wearable ultrasound improves motor function in an MPTP mouse model of Parkinson's disease. IEEE Trans Biomed Eng 2019;66(11):3006–3013. https://doi.org/10.1109/TBME.2019.2899631

81. Yuan Y, Zhao Z, Wang Z, Wang X, Yan J, Li X. The effect of low-intensity transcranial ultrasound stimulation on behavior in a mouse model of Parkinson's disease induced by MPTP. IEEE Trans. Neural Syst. Rehab. Eng. 2020;28(4):1017–1021. https://doi.org/10.1109/tnsre.2020.2978865

82. Xu T, Lu X, Peng D, et al. Ultrasonic stimulation of the brain to enhance the release of dopamine – a potential novel treatment for Parkinson's disease. Ultrason Sonochem 2020;63 December 2019:104955. https://doi.org/10.1016/j.ultsonch.2019.104955

83. Dong Y, Liu D, Zhao Y, et al. Assessment of neuroprotective effects of low-intensity transcranial ultrasound stimulation in a Parkinson's disease rat model by fractional anisotropy and relaxation time T2* value. Front Neurosci 2021;15:1–10. https://doi.org/10.3389/fnins.2021.590354

84. Chen X, Wang D, Zhang L, et al. Neuroprotective effect of low-intensity pulsed ultrasound on the mouse MPTP/MPP+ model of dopaminergic neuron injury. Ultrasound Med Biol 2021;47(8):2321–2330. https://doi.org/10.1016/j.ultrasmedbio.2021.03.034

85. Zhou H, Meng L, Xia X, et al. Transcranial ultrasound stimulation suppresses neuroinflammation in a chronic mouse model of Parkinson's disease. IEEE Trans Biomed Eng 2021;68(11):3375–3387. https://doi.org/10.1109/TBME.2021.3071807

86. Sung C-Y, Chiang P-K, Tsai C-W, Yang F-Y. Low-intensity pulsed ultrasound enhances neurotrophic factors and alleviates neuroinflammation in a rat model of Parkinson's disease. Cereb. Cortex 2021;32(1):176–185. https://doi.org/10.1093/cercor/bhab201

87. Samuel N, Ding MYR, Sarica C, et al. Accelerated transcranial ultrasound neuromodulation in Parkinson's disease: a pilot study. Mov Disord 2023;38(12):2209–2216. https://doi.org/10.1002/mds.29622

88. Grippe T, Shamli-Oghli Y, Darmani G, et al. Plasticity-induced effects of theta burst transcranial ultrasound stimulation in Parkinson's disease. Mov Disord 2024;39:1364–1374. https://doi.org/10.1002/mds.29836

89. Hu C, Zhang L, Luo G, Yao H, Song X, Liu Z. Clinical efficacy of low-intensity pulsed ultrasound in Parkinson's disease with cognitive impairment. J Neurophysiol 2024;132(5):1633–1638. https://doi.org/10.1152/jn.00323.2024

90. Darmani G, Ramezanpour H, Sarica C, et al. Individualized non-invasive deep brain stimulation of the basal ganglia using transcranial ultrasound stimulation. Nat Commun 2025;16(1):2693. https://doi.org/10.1038/s41467-025-57883-7

91. Ammi AY, Mast TD, Huang IH, Abruzzo TA, Coussios CC, Shaw GJ, Holland CK. Characterization of ultrasound propagation through ex-vivo human temporal bone. Ultrasound Med Biol 2008;34(10):1578–1589. https://doi.org/10.1016/j.ultrasmedbio.2008.02.012

92. Klein-Flügge MC, Fouragnan EF, Martin E. The importance of acoustic output measurement and monitoring for the replicability of transcranial ultrasonic stimulation studies. Brain Stimul 2024;17(1):32–34. https://doi.org/10.1016/j.brs.2023.12.002

93. Fong PY, Kop BR, Evans C, et al. Failed Double-Blind Replication of Offline 5Hz-rTUS-Induced Corticospinal Excitability; Preprint posted online November 26 2024. https://doi.org/10.1101/2024.11.25.625187.

94. Johnstone A, Nandi T, Martin E, Bestmann S, Stagg C, Treeby B. A range of pulses commonly used for human transcranial ultrasound stimulation are clearly audible. Brain Stimul 2021;14(5):1353–1355. https://doi.org/10.1016/j.brs.2021.08.015

95. Fomenko A, Chen KHS, Nankoo JF, et al. Systematic examination of low-intensity ultrasound parameters on human motor cortex excitability and behavior. Elife 2020;9:e54497. https://doi.org/10.7554/eLife.54497

96. Heimbuch IS, Fan TK, Wu AD, Faas GC, Charles AC, Iacoboni M. Ultrasound stimulation of the motor cortex during tonic muscle contraction Chen R, ed. PLoS One 2022;17(4):e0267268. https://doi.org/10.1371/journal.pone.0267268

97. Bancel T, Tiennot T, Aubry JF. Adaptive ultrasound focusing through the cranial bone for non-invasive treatment of brain disorders. In: Laugier P, Grimal Q, eds. Bone Quantitative Ultrasound. Vol 1364. Advances in Experimental Medicine and Biology. Cham: Springer International Publishing; 2022:397–409. https://doi.org/10.1007/978-3-030-91979-5_18.

98. Bancel T, Béranger B, Daniel M, et al. Sustained reduction of essential tremor with low-power non-thermal transcranial focused ultrasound stimulations in humans. Brain Stimul 2024;17(3):636–647. https://doi.org/10.1016/j.brs.2024.05.003

99. Przedborski S, Jackson-Lewis V, Djaldetti R, Liberatore G, Vila M, Vukosavic S, Almer G. The parkinsonian toxin MPTP: action and mechanism. Restor Neurol Neurosci 2000;16(2):135–142.

100. Simola N, Morelli M, Carta AR. The 6-hydroxydopamine model of Parkinson's disease. Neurotox Res 2007;11(3–4):151–167. https://doi.org/10.1007/BF03033565

101. Stocchi F, Bravi D, Emmi A, Antonini A. Parkinson disease therapy: current strategies and future research priorities. Nat Rev Neurol 2024;20(12):695–707. https://doi.org/10.1038/s41582-024-01034-x

102. Magalhães P, Lashuel HA. Opportunities and challenges of alpha-synuclein as a potential biomarker for Parkinson's disease and other synucleinopathies. NPJ Parkinsons Dis 2022;8(1):93. https://doi.org/10.1038/s41531-022-00357-0

103. Klæstrup IH, Just MK, Holm KL, Alstrup AKO, Romero-Ramos M, Borghammer P, van den Berge N. Impact of aging on animal models of Parkinson's disease. Front Aging Neurosci 2022;14:909273. https://doi.org/10.3389/fnagi.2022.909273

104. Musacchio T, Rebenstorff M, Fluri F, Brotchie JM, Volkmann J, Koprich JB, Ip CW. Subthalamic nucleus deep brain stimulation is neuroprotective in the A53T α-synuclein Parkinson's disease rat model. Ann Neurol 2017;81(6):825–836. https://doi.org/10.1002/ana.24947

105. Kordower JH, Olanow CW, Dodiya HB, et al. Disease duration and the integrity of the nigrostriatal system in Parkinson's disease. Brain 2013;136(8):2419–2431. https://doi.org/10.1093/brain/awt192

106. McDannold N, Vykhodtseva N, Hynynen K. Use of ultrasound pulses combined with Definity for targeted blood-brain barrier disruption: a feasibility study. Ultrasound Med Biol 2007;33(4):584–590. https://doi.org/10.1016/j.ultrasmedbio.2006.10.004

107. Wu SK, Chu PC, Chai WY, et al. Characterization of different microbubbles in assisting focused ultrasound-induced blood-brain barrier opening. Sci Rep 2017;7(1):46689. https://doi.org/10.1038/srep46689

108. Gattegno R, Arbel L, Riess N, Shinar H, Katz S, Ilovitsh T. Enhanced capillary delivery with nanobubble-mediated blood-brain barrier opening and advanced high resolution vascular segmentation. J Control Release 2024;369:506–516. https://doi.org/10.1016/j.jconrel.2024.04.001

109. Burgess A, Dubey S, Yeung S, Hough O, Eterman N, Aubert I, Hynynen K. Alzheimer disease in a mouse model: MR imaging–guided focused ultrasound targeted to the hippocampus opens the blood-brain barrier and improves pathologic abnormalities and behavior. Radiology 2014;273(3):736–745. https://doi.org/10.1148/radiol.14140245

110. Jordão JF, Thévenot E, Markham-Coultes K, et al. Amyloid-β plaque reduction, endogenous antibody delivery and glial activation by brain-targeted, transcranial focused ultrasound. Exp Neurol 2013;248:16–29. https://doi.org/10.1016/j.expneurol.2013.05.008

111. Leinenga G, Götz J. Scanning ultrasound removes amyloid-b and restores memory in an Alzheimer's disease mouse model. Sci Transl Med 2015;7(278):278ra33 https://doi.org/10.1126/scitranslmed.aaa2512

112. Scarcelli T, Jordão JF, O'Reilly MA, Ellens N, Hynynen K, Aubert I. Stimulation of hippocampal neurogenesis by transcranial focused ultrasound and microbubbles in adult mice. Brain Stimul 2014;7(2):304–307. https://doi.org/10.1016/j.brs.2013.12.012. Stimulation

113. Aarsland D, Batzu L, Halliday GM, Geurtsen GJ, Ballard C, Ray Chaudhuri K, Weintraub D. Parkinson disease-associated cognitive impairment. Nat Rev Dis Primers 2021;7(1):47. https://doi.org/10.1038/s41572-021-00280-3

114. Park SH, Baik K, Jeon S, Chang WS, Ye BS, Chang JW. Extensive frontal focused ultrasound mediated blood–brain barrier opening for the treatment of Alzheimer's disease: a proof-of-concept study. Transl Neurodegener 2021;10(1):1–11. https://doi.org/10.1186/s40035-021-00269-8

115. Hirano S, Eckert T, Flanagan T, Eidelberg D. Metabolic networks for assessment of therapy and diagnosis in Parkinson's disease. Mov Disord 2009;24 Suppl 2(0 2):S725–S731. https://doi.org/10.1002/mds.22541

116. Blesa J, Pineda-pardo JA, Inoue K i, et al. BBB opening with focused ultrasound in nonhuman primates and Parkinson's disease patients: targeted AAV vector delivery and PET imaging. Sci Adv 2023;9(16):1–13. https://doi.org/10.1126/sciadv.adf4888

117. Gasca-Salas C, Pineda-Pardo JA, Del Álamo M, et al. Nigrostriatal blood-brain barrier opening in Parkinson's disease. J Neurol Neurosurg PsychiatryPublished online May 17 2024;95(11):1089–1092. https://doi.org/10.1136/jnnp-2023-332967

118. Niu J, Xie J, Guo K, et al. Efficient treatment of parkinson's disease using ultrasonography-guided rhfgf20 proteoliposomes. Drug Deliv 2018;25(1):1560–1569. https://doi.org/10.1080/10717544.2018.1482972

119. Feng Y, An R, Zhang Y, Chen M, Wang L, Duan Y, Xing C. AHNAK-modified microbubbles for the intracranial delivery of triptolide: in-vitro and in-vivo investigations. Int J Pharm 2022;629-(July):122351. https://doi.org/10.1016/j.ijpharm.2022.122351

120. Fan CH, Ting CY, Lin CY, et al. Noninvasive, targeted, and non-viral ultrasound-mediated GDNF-plasmid delivery for treatment of Parkinson's disease. Sci Rep 2016;6:19579. https://doi.org/10.1038/srep19579

121. Xhima K, Nabbouh F, Hynynen K, Aubert I, Tandon A. Noninvasive delivery of an α -synuclein gene silencing vector with magnetic resonance – guided focused ultrasound. Mov Disord 2018;33(10):1567–1579. https://doi.org/10.1002/mds.101

122. Yan Y, Chen Y, Liu Z, et al. Brain delivery of curcumin through low-intensity ultrasound-induced blood–brain barrier opening via lipid-plga nanobubbles. Int J Nanomedicine 2021;16(November):7433–7447. https://doi.org/10.2147/IJN.S327737

123. Karakatsani ME, Wang S, Samiotaki G, et al. Amelioration of the nigrostriatal pathway facilitated by ultrasound-mediated neurotrophic delivery in early Parkinson's disease. J Control Release 2019;303(March):289–301. https://doi.org/10.1016/j.jconrel.2019.03.030

124. Long L, Cai X, Guo R, et al. Treatment of Parkinson's disease in rats by Nrf2 transfection using MRI-guided focused ultrasound delivery of nanomicrobubbles. Biochem Biophys Res Commun 2017;482(1):75–80. https://doi.org/10.1016/j.bbrc.2016.10.141

125. Lin CY, Lin YC, Huang CY, Wu SR, Chen CM, Liu HL. Ultrasound-responsive neurotrophic factor-loaded microbubble- liposome complex: preclinical investigation for Parkinson's disease treatment. J Control Release 2020;321(February):519–528. https://doi.org/10.1016/j.jconrel.2020.02.044

126. Mead BP, Kim N, Miller GW, et al. Novel focused ultrasound gene therapy approach noninvasively restores dopaminergic neuron function in a rat Parkinson's disease model. Nano Lett 2017;17(6):3533–3542. https://doi.org/10.1021/acs.nanolett.7b00616

127. Zhang N, Yan F, Liang X, et al. Localized delivery of curcumin into brain with polysorbate 80-modified cerasomes by ultrasound-targeted microbubble destruction for improved Parkinson's disease therapy. Theranostics 2018;8(8):2264–2277. https://doi.org/10.7150/thno.23734

128. Lin CY, Hsieh HY, Chen CM, et al. Non-invasive, neuron-specific gene therapy by focused ultrasound-induced blood-brain barrier opening in Parkinson's disease mouse model. J Control Release 2016;235:72–81. https://doi.org/10.1016/j.jconrel.2016.05.052

129. Yue P, Miao W, Gao L, Zhao X, Teng J. Ultrasound-triggered effects of the microbubbles coupled to GDNF plasmid-loaded PEGylated liposomes in a rat model of Parkinson's disease. Front. Neurosci 2018b;12. https://doi.org/10.3389/fnins.2018.00222

130. Yue P, Gao L, Wang X, Ding X, Teng J. Ultrasound-triggered effects of the microbubbles coupled to GDNF- and Nurr1-loaded PEGylated liposomes in a rat model of Parkinson's disease. J Cell Biochem 2018a;119(6):4581–4591. Portico. https://doi.org/10.1002/jcb.26608

131. Wu CY, Huang RY, Liao EC, et al. A preliminary study of Parkinson's gene therapy via sono-magnetic sensing gene vector for conquering extra/intracellular barriers in mice. Brain Stimul 2020; 13(3):786–799. https://doi.org/10.1016/j.brs.2020.02.024

132. Trinh D, Nash J, Goertz D, Hynynen K, Bulner S, Iqbal U, Keenan J. Microbubble drug conjugate and focused ultrasound blood brain barrier delivery of AAV-2 SIRT-3. Drug Deliv. 2022; 29(1):1176–1183. https://doi.org/10.1080/10717544.2022.2035855

133. Wang X, Cui G, Yang X, et al. Intracerebral administration of ultrasound-induced dissolution of lipid-coated GDNF microbubbles provides neuroprotection in a rat model of Parkinson's disease. Brain Res. Bull. 2014;103:60–65. https://doi.org/10.1016/j.brainresbull.2014.02.006

134. Ji R, Smith M, Niimi Y, et al. Focused ultrasound enhanced intranasal delivery of brain derived neurotrophic factor produces neurorestorative effects in a Parkinson's disease mouse model. Sci Rep 2019;9(1):1–13. https://doi.org/10.1038/s41598-019-55294-5

135. Wang Y, Luo K, Li J, et al. Focused ultrasound promotes the delivery of Gastrodin and enhances the protective effect on dopaminergic neurons in a mouse model of Parkinson's disease. Front Cell Neurosci 2022;16(May):1–13. https://doi.org/10.3389/fncel.2022.884788

136. Menon S, Kofoed RH, Nabbouh F, et al. Viral alpha-synuclein knockdown prevents spreading synucleinopathy. Brain Commun 2021;3(4):fcab247. https://doi.org/10.1093/braincomms/fcab247

137. Zhang H, Sierra C, Karakatsani ME, Jackson-Lewis VR, Przedborski S, Konofagou E. Focused-ultrasound mediated anti-alpha-synuclein antibody delivery for the treatment of Parkinson's disease. Kobe, Japan: IEEE International Ultrasonics Symposium (IUS); 2018:1–4. https://doi.org/10.1109/ULTSYM.2018.8579677

138. Nisbet RM, Jeugd AVD, Leinenga G, Evans HT, Janowicz PW, Götz J. Combined effects of scanning ultrasound and a tau-specific single chain antibody in a tau transgenic mouse model. Brain 2017;140:1220–1230. https://doi.org/10.1093/brain/awx052

139. Menon S, Armstrong S, Hamzeh A, Visanji NP, Sardi SP, Tandon A. Alpha-synuclein targeting therapeutics for Parkinson's disease and related Synucleinopathies. Front Neurol 2022;13: 852003. https://doi.org/10.3389/fneur.2022.852003

140. Whone A, Luz M, Boca M, et al. Randomized trial of intermittent intraputamenal glial cell line-derived neurotrophic factor in Parkinson's disease. Brain 2019;142(3):512–525. https://doi.org/10.1093/brain/awz023

141. Olanow CW, Bartus RT, Baumann TL, et al. Gene delivery of neurturin to putamen and substantia nigra in Parkinson disease: a double-blind, randomized, controlled trial. Ann Neurol 2015; 78(2):248–257. https://doi.org/10.1002/ana.24436

142. Chu Y, Bartus RT, Manfredsson FP, Olanow CW, Kordower JH. Long-term post-mortem studies following neurturin gene therapy in patients with advanced Parkinson's disease. Brain 2020;143(3): 960–975. https://doi.org/10.1093/brain/awaa020

143. Krishna V, Fishman PS, Eisenberg HM, et al. Trial of globus pallidus focused ultrasound ablation in Parkinson's disease. N Engl J Med 2023;388(8):683–693. https://doi.org/10.1056/NEJMoa2202721

144. Martínez-Fernández R, Máñez-Miró JU, Rodríguez-Rojas R, et al. Randomized trial of focused ultrasound subthalamotomy for Parkinson's disease. N Engl J Med 2020;383(26):2501–2513. https://doi.org/10.1056/NEJMoa2016311

145. Bond AE, Shah BB, Huss DS, et al. Safety and efficacy of focused ultrasound thalamotomy for patients with medication-refractory, tremor-dominant Parkinson disease: a randomized clinical trial. JAMA Neurol 2017;74(12):1412–1418. https://doi.org/10.1001/jamaneurol.2017.3098

146. Martínez-Fernández R, Natera-Villalba E, Máñez Miró JU, et al. Prospective Long-term follow-up of focused ultrasound unilateral subthalamotomy for Parkinson disease. Neurology 2023;100(13): e1395–e1405. https://doi.org/10.1212/WNL.0000000000206771

147. Paschen S, Natera-Villalba E, Pineda-Pardo JA, et al. Comparative study of focused ultrasound unilateral thalamotomy and subthalamotomy for medication-refractory Parkinson's disease tremor. Mov Disord 2025;40(5):823–833. https://doi.org/10.1002/mds.30159

148. Kaplitt MG, Krishna V, Eisenberg HM, et al. Safety and efficacy of staged, bilateral focused ultrasound thalamotomy in essential tremor: An open-label clinical trial. JAMA Neurol 2024;81(9): 939–946. https://doi.org/10.1001/jamaneurol.2024.2295

149. Campins-Romeu M, Conde-Sardón R, Sastre-Bataller I, et al. Safety and efficacy of bilateral staged focused ultrasound thalamotomy in refractory essential tremor. Brain Commun 2025; 7(3):fcaf168. https://doi.org/10.1093/braincomms/fcaf168

150. McDannold N, White PJ, Cosgrove R. Elementwise approach for simulating transcranial MRI-guided focused ultrasound thermal ablation. Phys Rev Res 2019;1(3):033205. https://doi.org/10.1103/physrevresearch.1.033205

151. Windels F, Thevathasan W, Silburn P, Sah P. Where and what is the PPN and what is its role in locomotion? Brain 2015;138(Pt 5): 1133–1134. https://doi.org/10.1093/brain/awv059

152. Wagle Shukla A, Bange M, Muthuraman M. Patient, target, device, and program selection for DBS in Parkinson's disease: advancing toward precision care. NPJ Parkinsons Dis 2025;11(1):195. https://doi.org/10.1038/s41531-025-01015-x

153. Blomstedt P, Hariz GM, Hariz MI. Pallidotomy versus pallidal stimulation. Parkinsonism Relat Disord 2006;12(5):296–301. https://doi.org/10.1016/j.parkreldis.2005.12.007

154. Martínez Fernández R, Natera Villalba E, Rodriguez-Rojas R, et al. Unilateral focused ultrasound subthalamotomy in early Parkinson's disease: a pilot study. J Neurol Neurosurg Psychiatry 2024;95(3):206–213. https://doi.org/10.1136/jnnp-2023-331211

155. Elabi OF, Pass R, Sormonta I, et al. Human embryonic stem cell-derived dopaminergic grafts alleviate L-DOPA induced dyskinesia. J Parkinsons Dis 2022;12(6):1881–1896. https://doi.org/10.3233/JPD-212920

156. Kirkeby A, Parmar M, Barker RA. Strategies for bringing stem cell-derived dopamine neurons to the clinic: a European approach (STEM-PD). Prog Brain Res. The Netherlands: Elsevier; Vol. 230; 2017:165–190. https://doi.org/10.1016/bs.pbr.2016.11.011.

157. Cho SE, Kim YM, Jeong JS, Seo YK. The effect of ultrasound for increasing neural differentiation in hBM-MSCs and inducing neurogenesis in ischemic stroke model. Life Sci 2016;165:35–42. https://doi.org/10.1016/j.lfs.2016.08.029

158. Ning GZ, Song WY, Xu H, et al. Bone marrow mesenchymal stem cells stimulated with low-intensity pulsed ultrasound: better choice of transplantation treatment for spinal cord injury: treatment for SCI by LIPUS-BMSCs transplantation. CNS Neurosci Ther 2019; 25(4):496–508. https://doi.org/10.1111/cns.13071

159. Yao X, Wang W, Li Y, et al. Study of the mechanism by which MSCs combined with LITUS treatment improve cognitive dysfunction caused by traumatic brain injury. Neurosci Lett 2022;787: 136825. https://doi.org/10.1016/j.neulet.2022.136825

160. Burgess A, Ayala-Grosso CA, Ganguly M, Jordão JF, Aubert I, Hynynen K. Targeted delivery of neural stem cells to the brain using MRI-guided focused ultrasound to disrupt the blood-brain barrier. PLoS One 2011;6(11):e27877. https://doi.org/10.1371/journal.pone.0027877

161. Lee J, Chang WS, Shin J, et al. Non-invasively enhanced intracranial transplantation of mesenchymal stem cells using focused ultrasound mediated by overexpression of cell-adhesion molecules. Stem Cell Res 2020;43:101726. https://doi.org/10.1016/j.scr.2020.101726

162. Shen WB, Anastasiadis P, Nguyen B, Yarnell D, Yarowsky PJ, Frenkel V, Fishman PS. Magnetic enhancement of stem cell-targeted delivery into the brain following MR-guided focused ultrasound for opening the blood-brain barrier. Cell Transplant 2017;26(7):1235–1246. https://doi.org/10.1177/0963689717715824

163. Zhu Q, Xu X, Chen B, et al. Ultrasound-targeted microbubbles destruction assists dual delivery of beta-amyloid antibody and neural stem cells to restore neural function in transgenic mice of Alzheimer's disease. Med Phys 2022;49(3):1357–1367. https://doi.org/10.1002/mp.15500

164. Wu SK, Tsai CL, Mir A, Hynynen K. MRI-guided focused ultrasound for treating Parkinson's disease with human mesenchymal

stem cells. Sci Rep 2025;15(1):2029. https://doi.org/10.1038/s41598-025-85811-8

165. Okkels N, Horsager J, Labrador-espinosa M, et al. Severe cholinergic terminal loss in newly diagnosed dementia with Lewy bodies. Brain 2023;146:3690–3704.

166. Shin J, Kong C, Lee J, et al. Focused ultrasound-induced blood-brain barrier opening improves adult hippocampal neurogenesis and cognitive function in a cholinergic degeneration dementia rat model. Alzheimer's Res Ther 2019;11(1):1–15. https://doi.org/10.1186/s13195-019-0569-x

167. Xhima K, Markham-coultes K, Kofoed RH, Saragovi HU, Hynynen K, Aubert I. Ultrasound delivery of a TrkA agonist confers neuroprotection to Alzheimer-associated pathologies. Brain 2021;145(8):2806–2822.

168. Xhima K, Markham-Coultes K, Nedev H, Heinen S, Saragovi HU, Hynynen K, Aubert I. Focused ultrasound delivery of a selective TrkA agonist rescues cholinergic function in a mouse model of Alzheimer's disease. Sci Adv 2020;6(4):eaax6646. https://doi.org/10.1126/sciadv.aax6646

169. Hatch RJ, Leinenga G, Götz J. Scanning ultrasound (SUS) causes no changes to neuronal excitability and prevents age-related reductions in hippocampal CA1 dendritic structure in wild-type mice. PLoS One 2016;11(10):1–14. https://doi.org/10.1371/journal.pone.0164278

170. Delpech JC, Madore C, Nadjar A, Joffre C, Wohleb ES, Layé S. Microglia in neuronal plasticity: influence of stress. Neuropharmacology 2015;96:19–28. https://doi.org/10.1016/j.neuropharm.2014.12.034 Pt A

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.