

Physical and Device-Based Regenerative Therapies for Cognitive Decline in Neurodegenerative Disease: A Critical Narrative Review of Oscillatory, Photonic, Electromagnetic and Acoustic Neuromodulation

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Abstract

Background: Non-pharmacological, device-based “physical regenerative” therapies — gamma and alpha oscillatory entrainment, transcranial photobiomodulation (PBM), transcranial electrical and magnetic stimulation, pulsed electromagnetic fields (PEMF), focused ultrasound (FUS), transcranial pulse stimulation (TPS) and extracorporeal shockwave therapy (ESWT) — are increasingly marketed for Alzheimer’s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS) and age-related dementia. Their proposed mechanisms converge on endogenous regenerative biology: mitochondrial bioenergetics, neurotrophin signalling, microglial phenotype switching, glymphatic clearance and adult neural stem/progenitor cell (NSPC) activation. Claims frequently outpace the controlled evidence.

Methods: Narrative critical review. PubMed/MEDLINE, Cochrane Library, ClinicalTrials.gov and regulatory dossiers (FDA) were searched through February 2026 for preclinical and clinical studies of each modality in AD, mild cognitive impairment (MCI), PD, ALS and vascular/mixed dementia. Randomised sham-controlled trials, meta-analyses and regulatory documents were prioritised; effect sizes, primary-endpoint status and risk of bias were extracted. Retracted publications were identified and excluded from the evidence base.

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Results: Across modalities the preclinical regenerative signal is strong and mechanistically coherent, but clinical translation is uneven. Repetitive transcranial magnetic stimulation (rTMS) has the most robust cognitive evidence in AD/MCI (pooled SMD ≈ 0.77), supported by two positive randomised trials of network-targeted protocols; nevertheless the only device to reach a formal FDA advisory review for AD was found safe but not effective. Transcranial PBM produced the largest single randomised effect reported to date in MCI due to AD (MoCA-K +3.87 vs -0.74, $p < 0.001$), yet trials in PD were negative and one favoured sham. Gamma sensory stimulation (GENUS) has compelling rodent data — including aquaporin-4-dependent glymphatic amyloid clearance — but two independent laboratories failed to replicate entrainment and amyloid reduction, the pivotal-stage OVERTURE trial missed all three primary endpoints, and a 2025 meta-analysis of 11 studies found no cognitive benefit (SMD 0.16, $p = 0.55$). tDCS shows a modest overall benefit (SMD ≈ 0.39) driven by AD, with null results in MCI; gamma-tACS results are contradictory (one positive home-based randomised trial versus two negative controlled trials). Transcranial electromagnetic treatment rests on a single open-label series of eight patients. FUS reliably and reversibly opens the blood–brain barrier but has produced no randomised evidence and no cognitive benefit. The largest TPS randomised trial missed its primary endpoint. No human trial of ESWT for cognition or any neurodegenerative disease exists, and evidence in ALS is minimal for every modality.

Conclusions: Device-based neuromodulation is biologically plausible, generally safe and, for rTMS and possibly PBM, supported by replicated positive randomised data; it is not yet a validated disease-modifying regenerative therapy. Honest communication requires distinguishing mechanism from outcome, secondary from primary endpoints, breakthrough designation from approval, and absence of evidence from evidence of absence.

Keywords

Photobiomodulation; Gamma entrainment; Transcranial magnetic stimulation; Neural stem cells; Alzheimer disease; Neuromodulation.

Introduction

Neurodegenerative disorders with cognitive deficits — AD, PD dementia, ALS with frontotemporal involvement and age-related (“senile”) dementia — remain therapeutically unsatisfying. Anti-amyloid immunotherapies have achieved statistically significant but clinically modest slowing of decline at the cost of amyloid-related imaging abnormalities, infusion burden and expense. Against this backdrop, a heterogeneous family of non-invasive physical therapies has attracted intense clinical, commercial and patient interest. They share three features: they deliver energy (photons, electrons, magnetic flux, acoustic pressure) rather than molecules; they are largely non-invasive and repeatable at home or in outpatient settings; and they are proposed to act by restoring endogenous repair capacity rather than by clearing a single pathological protein.

This last claim places them squarely within regenerative medicine. The mechanisms invoked — cytochrome c oxidase photoactivation and mitochondrial ATP recovery, BDNF/TrkB-dependent synaptic plasticity, microglial M1→M2 repolarisation, exosomal signalling, glymphatic clearance and, most directly, the proliferation and differentiation of adult NSPCs in the subgranular and subventricular zones — are the same pathways targeted by cell-based and secretome-based therapies. Physical energy may therefore be understood as a non-cellular means of manipulating the endogenous stem cell niche.

The field is also unusually vulnerable to premature enthusiasm. Devices reach patients through pathways (CE marking, FDA Breakthrough Device Designation, wellness exemptions, direct-to-consumer sales) that do not require demonstration of clinical efficacy. Positive mouse data, single-arm case series and secondary endpoints are routinely presented to patients as proof of benefit. Physicians practising regenerative medicine are frequently asked to adjudicate these claims.

This review therefore has two aims. First, to synthesise, modality by modality and disease by disease, the best available preclinical and clinical evidence for oscillatory, photonic, electromagnetic and acoustic neuromodulation in neurodegenerative cognitive impairment. Second, to apply an explicit critical filter — primary versus secondary endpoints, replication status, blinding integrity, regulatory reality and retraction status — so that the resulting map is usable for clinical decision-making and for the design of the trials the field still needs.

Methods

This is a narrative critical review, not a systematic review, and was conducted without a registered protocol. PubMed/MEDLINE, the Cochrane Database of Systematic Reviews, ClinicalTrials.gov and publicly available FDA advisory-committee and guidance documents were searched from inception to February 2026. Search terms combined each modality (gamma entrainment, GENUS, 40 Hz, flicker, alpha oscillation, neurofeedback, photobiomodulation, low-level light therapy, near-infrared, transcranial direct current stimulation, transcranial alternating current stimulation, transcranial random noise stimulation, transcutaneous auricular vagus nerve stimulation, repetitive transcranial magnetic stimulation, theta-burst stimulation, pulsed electromagnetic field, transcranial electromagnetic treatment, focused ultrasound, blood-brain barrier opening, transcranial pulse stimulation, extracorporeal shockwave therapy, whole-body vibration, cranial electrotherapy stimulation) with each condition (Alzheimer disease, mild cognitive impairment, dementia, Parkinson disease, amyotrophic lateral sclerosis, vascular cognitive impairment) and with mechanistic terms (neural stem cell, neurogenesis, BDNF, microglia, exosome, glymphatic).

Priority was given, in descending order, to (i) randomised sham- or placebo-controlled trials and their meta-analyses, (ii) regulatory dossiers, (iii) prospective open-label studies, (iv) mechanistic animal and in-vitro work. For every clinical trial cited, the pre-specified primary endpoint and its result were recorded separately from secondary and exploratory outcomes. Reference lists and the Retraction Watch database were checked; two publications frequently cited in this field have been retracted and are identified as such in the text so that readers do not propagate them as evidence.

Ethics statement. This work is a review of previously published literature. It involved no human participants, no identifiable patient data, no animal experimentation and no interventional procedure. Under Brazilian Resolution CNS 466/2012 and CNS 510/2016, and under international norms for research not involving human subjects, no institutional review board / research ethics committee (CEP/CONEP) approval and no informed consent were required.

Mechanistic Framework: Physical Energy as a Regenerative Stimulus

Five convergent mechanisms recur across otherwise dissimilar modalities and provide the conceptual link to stem cell biology (**Table 1**).

- **Bioenergetics:** Red and near-infrared photons (600–1100 nm) are absorbed by cytochrome c oxidase, dissociating inhibitory nitric oxide, increasing electron transport, ATP synthesis and a controlled burst of reactive oxygen species that acts as a redox second messenger [1]. The dose–

response is biphasic: insufficient or excessive fluence yields no effect or inhibition, which explains much of the heterogeneity in the clinical literature [3].

- **Neurotrophin-dependent plasticity:** Anodal direct current stimulation induces long-term potentiation only in the presence of intact BDNF/TrkB signalling; it fails in *Bdnf* and *TrkB* knockouts and in human carriers of the Val66Met polymorphism [4]. PBM at 660 nm increases hippocampal BDNF while reducing oxidative stress [5]. Neurotrophin upregulation is thus a shared final common path for photonic and electrical stimulation.
- **Adult neurogenesis and the NSPC niche:** This is the most direct point of contact with stem cell science. Multisession anodal tDCS expands type-1 radial-glia-like, type-2a and type-2b progenitor populations in the mouse dentate gyrus and improves context discrimination [6]. rTMS promotes subventricular zone NSPC proliferation through miR-25 regulation [7]. Transcranial focused ultrasound with microbubbles stimulates hippocampal neurogenesis in adult mice [8]. PBM restores the Sox2-positive NSC pool in aged 3xTg-AD mice [9]. Multisensory gamma stimulation enhances adult neurogenesis in Down syndrome model mice and in ageing mice [10]. PEMF drives human bone-marrow mesenchymal stromal cell (MSC) proliferation and, in 2025 work, iPSC-derived neuronal maturation through cholesterol biosynthesis [12].
- **Immunomodulation and the secretome:** 1070 nm light shifts microglia from M1 to M2; exosomes derived from these light-modulated M2 microglia, carrying miR-7670-3p, improved cognition when transferred to AD model mice — a direct demonstration that a physical stimulus can generate a therapeutic cell-free secretome [14]. Rotating magnetic fields similarly regulate microglial polarisation in a sporadic AD model [15], and transcranial electromagnetic treatment has been proposed to “rebalance” blood and brain cytokines [16].
- **Clearance:** Gamma stimulation increases cerebrospinal fluid influx and interstitial efflux in mice; the effect depends on aquaporin-4 in astrocytic endfeet and on vasoactive intestinal peptide interneurons, and drives amyloid out of the parenchyma along the glymphatic route [17]. Focused ultrasound with microbubbles achieves the same goal by a different mechanism — transient, reversible opening of the blood–brain barrier [18].

Mechanistic plausibility is therefore not the field’s weakness. Translation is.

Oscillatory Entrainment: Gamma and Alpha

Preclinical foundation

Non-invasive 40 Hz light flicker entrained hippocampal and visual cortical gamma, reduced A β 1-40 and A β 1-42 and induced a microglial morphological state consistent with enhanced phagocytosis [19]. Combined auditory and visual stimulation extended effects to prefrontal and hippocampal networks, reduced tau phosphorylation and neuronal loss, and improved recognition memory and spatial learning [21]. Later work added glymphatic clearance [17], remyelination in cuprizone-treated mice [23], sleep promotion via cortical adenosine [24], vibrotactile delivery [25] and reduced α -synuclein deposition in PD models [26].

Failed replications

Two independent groups reported negative findings. One found that 40 Hz light did not entrain native

gamma oscillations in AD model mice, produced no amyloid reduction and elicited responses better explained by evoked visual potentials than by true oscillatory entrainment [27]. The other exposed 5XFAD mice chronically to 24, 40 or 80 Hz flicker and found no reduction in amyloid load at any frequency [28]. These are not minor methodological quibbles; they challenge the central premise [29].

Clinical trials

Early feasibility work in prodromal and mild AD demonstrated tolerability, entrainment on EEG and preliminary functional connectivity changes [30–32]. The industry programme (Cognito Therapeutics) reported, in a 6-month randomised sham-controlled study of 76 participants, that all three pre-specified primary endpoints were not met [33]. The widely publicised results — a 77% reduction in functional decline on ADCS-ADL ($p=0.0004$) and 61–69% less whole-brain and ventricular volume loss — are secondary and exploratory outcomes, and the active group was on average six years younger at baseline than sham (69.7 vs 75.6 years, $p=0.009$), an imbalance that plausibly confounds atrophy comparisons [33]. Related reports of improved sleep, daily living and white-matter preservation derive from the same small dataset [34]. A pivotal trial of approximately 670 participants (NCT05637801) has a primary completion date of June 2026 and no reported results [36]. FDA Breakthrough Device Designation, granted in 2021, expedites review; it is not evidence of efficacy and not an approval.

An independent Danish randomised placebo-controlled pilot using invisible spectral flicker found the intervention safe and feasible without significant cognitive benefit [37], and the same group subsequently showed that stimulation anywhere between 36 and 44 Hz evokes comparable responses — undermining the notion that 40 Hz is uniquely therapeutic in humans [38]. An earlier PET study of 40 Hz light found no change in amyloid load [39].

The quantitative bottom line is provided by meta-analysis: pooling 11 studies and 341 patients, gamma auditory-visual stimulation produced no significant cognitive improvement (SMD 0.16, 95% CI –0.36 to 0.68, $p=0.55$) while increasing tinnitus risk (risk difference 0.16, $p=0.01$) [40]. A second 2025 meta-analysis reached similarly cautious conclusions [41]. Reviews from within the field acknowledge the gap between rodent and human data [42].

Alpha entrainment, binaural beats and rhythmic vibration

Alpha-band approaches are less developed. A randomised controlled trial of neurofeedback in MCI reported memory improvement [44]; theta-band binaural beat stimulation correlated with improved cognitive scores in AD patients in a small study [45]; rhythmic sensory stimulation at 40 Hz produced short-term exploratory benefits in AD and a case series in dementia [46]. Technical reviews emphasise poor standardisation of audio-visual entrainment protocols [48].

Parkinson's disease and ALS

In PD, a double-blind randomised trial of long-term 40 Hz physioacoustic vibration reported motor improvement [49]; binaural acoustic stimulation has been examined in small controlled work [50]; a trial of gamma flicker for freezing of gait is ongoing [51]. For ALS there is, at the time of writing, no published human study of gamma or alpha entrainment of any kind.

Photobiomodulation (Biophotostimulation)

Alzheimer's disease and MCI

The most rigorous evidence in this modality is recent. A randomised, double-blind, placebo-controlled confirmatory trial of home-based transcranial PBM (808 nm, 12 weeks) in 80 patients with MCI due to AD reported a between-group difference on the Korean MoCA of $+3.87 \pm 2.51$ versus -0.74 ± 2.85 ($p < 0.001$) [52], following an earlier sham-controlled study by the same group [53]. A multimodal pilot randomised trial added cognitive, metabolic and neuroimaging outcomes [54]. Earlier signals came from case series and small controlled pilots combining transcranial and intranasal delivery [55–58], and combined tDCS plus intranasal near-infrared stimulation has been piloted [59]; a Japanese sham-controlled protocol is in progress [60].

Meta-analyses of randomised trials estimate moderate effects on cognition (SMD approximately 0.51–0.66), with the caveats of small samples, heterogeneous devices and short follow-up [61–64]. Animal meta-analysis is consistent and shows dose dependence [65]. Comprehensive reviews of the preclinical base are available [66–68].

Parkinson's disease

Results are largely negative. A randomised placebo-controlled study of a transcranial PBM helmet in 40 patients found improvement in 23% of active versus 21% of sham participants [69]. A 2025 randomised trial with extended treatment in 63 patients found the MoCA favoured sham ($p = 0.015$) [70]. Positive claims rest on uncontrolled follow-up [71] and retrospective microbiome data [72]. Preclinically, remote abdominal or leg irradiation rescued approximately 80% of nigral dopaminergic neurons after MPTP insult in mice, suggesting a systemic, possibly circulating-mediator mechanism [73], consistent with a broader gut–brain literature [74] and with proposed opsin-dependent effects outside the eye [75].

ALS

The ALSUntangled group assigned light therapy a Trials grade of “U” (unknown) — no completed human trial supports its use in ALS [76].

The dosimetry problem

Transcranial penetration is the central unresolved issue. Cadaveric and modelling studies indicate that only about 0.2–10% of applied near-infrared irradiance reaches cortex, and intranasal delivery to deep structures is orders of magnitude lower [77–79]. Combined with the biphasic dose response [3], this means that two trials using “808 nm PBM” may deliver pharmacologically incomparable doses. Tolerability appears dose-dependent but favourable [80]; the FDA has issued draft guidance for PBM device submissions, reflecting regulatory recognition without efficacy endorsement for dementia [81]. In vitro, PBM exerts a classic biphasic effect on MSC proliferation, differentiation and migration, with pro-proliferative fluences in the low single-digit J/cm² range and suppression at high fluence [82] — a directly transferable lesson for clinical dosing.

Transcranial Electrical and Magnetic Stimulation

Transcranial direct current stimulation

A 2025 meta-analysis of 19 randomised trials (945 participants) found a significant overall benefit of tDCS

on cognition in older adults with cognitive impairment (SMD 0.39), with a larger effect in AD (0.91) [83], consistent with a second 2024 meta-analysis [84]. The picture in MCI alone is null: pooled MoCA change SMD 0.02 ($p=0.88$) [85], and the largest single randomised trial in mild neurocognitive disorder ($n=201$) was likewise unconvincing [86].

In PD a striking dissociation emerges: tDCS shows no reliable motor benefit (Hedges $g \approx -0.14$, $p=0.737$) but a moderate cognitive effect (SMD ≈ 0.73) [87], with feasibility demonstrated for remotely supervised home use paired with cognitive training [89].

In ALS early work found no modulation of motor cortex excitability [90], but a randomised double-blind sham-controlled trial of cortico-spinal tDCS in 31 patients reported reduced neurofilament light chain and a survival signal, followed by an open-label phase [91]; a 2025 systematic review concludes that the evidence remains preliminary [92].

Gamma transcranial alternating current stimulation

Single-session and short-course 40 Hz tACS improved episodic memory and restored cholinergic transmission indices in crossover studies in AD [93], and a case series suggested reduced tau burden on PET [95]. A 2025 randomised clinical trial of home-based gamma tACS reported a significant ADAS-Cog-13 advantage [96]. Against this, the TRANSFORM-AD randomised controlled trial was negative on its primary outcome ($p=0.449$) [97], and a high-definition 40 Hz tACS trial in mild AD was also negative ($p=0.897$) [98]. Meta-analyses and systematic reviews therefore describe the modality as promising but unresolved [99–101].

Other electrical approaches

Theta–gamma coupled tACS improved working memory in older adults with effects persisting up to a month, though in cognitively healthy cohorts [102]. Transcranial random noise stimulation combined with cognitive training in healthy older adults produced limited benefit [104]. Transcutaneous auricular vagus nerve stimulation in PD has been tested in a randomised sham-controlled trial with modest results [105]. Cranial electrotherapy stimulation has no dementia evidence; its largest randomised trial, in depression, was negative ($p=0.46$) [106].

Repetitive transcranial magnetic stimulation

rTMS carries the strongest cognitive evidence of any modality reviewed here. Meta-analysis in MCI and AD yields SMD 0.77 [108], with mean differences of approximately 1.8 points on the MMSE and 2.7 points on ADAS-Cog in subsequent pooled analyses [109]. Two randomised trials with anatomically or network-targeted protocols support this: precuneus rTMS in 50 AD patients slowed CDR-SB progression (group $\times$ time $p=0.009$) with 52-week extension data [111], and personalised hippocampal-network-targeted rTMS improved ADAS-Cog by 5.2 points ($p=0.002$) [113]. Accelerated intermittent theta-burst stimulation broadly improved symptoms and cognition in a randomised trial [114]. In PD, rTMS improves motor symptoms (SMD 0.42–0.53) [115]. In ALS, a randomised trial of 80 patients reported an ECAS improvement of 2.24 points ($p=0.031$) [116], while the Cochrane review of rTMS in ALS concluded that evidence is insufficient [117]. In small-vessel vascular cognitive impairment, rTMS added to donepezil outperformed donepezil alone [118].

The essential counterweight is regulatory. The neuroAD Therapy System (rTMS plus cognitive training) underwent FDA De Novo review; the agency's executive summary concluded that the device was safe but that effectiveness was not demonstrated — the primary endpoint numerically favoured sham by 1.45 points ($p=0.09$) [119]. Positive meta-analytic effect sizes in this literature therefore coexist with a failed regulatory trial, a pattern typical of small-study bias.

Consensus safety and application guidelines exist for all three families [120-124], and a 2025 Nature Reviews Neurology synthesis provides the current expert framing [125]. Note that one frequently cited paper linking rTMS to BDNF elevation (Zhao et al., *J Int Med Res*, 2019) has been retracted and should not be used to support mechanistic claims.

Electromagnetic Fields, Ultrasound, Shockwaves and Other Devices

Transcranial electromagnetic treatment and PEMF

The entire clinical evidence base for transcranial electromagnetic treatment (TEMT; MemorEM) consists of one open-label study of eight AD patients, in which the whole-group ADAS-cog change did not reach significance ($p=0.09$) and the reported benefit derives from a responder subgroup (effect size 1.21, $p<0.02$) [126], plus cytokine analyses [16] and a 2½-year extension in five patients reporting a 57% fall in CSF p-tau217 ($p=0.031$) [127]. FDA Breakthrough Device Designation was granted in 2020; no randomised controlled trial has been published. PEMF's regenerative credentials are mainly in vitro: proliferation increases of 40–59% in human bone-marrow MSCs with upregulated osteogenic transcription factors [12,128], calcium-dependent osteogenic differentiation [129], ERK/CREB-mediated neurodifferentiation with benefit in cerebral ischaemia models [130] and cholesterol-biosynthesis-dependent maturation of iPSC-derived neurons at 1 mT/15 Hz [13]. None of this has been translated to dementia. Peripheral nerve regeneration is a more mature application [131], and static magnetic stimulation of the CNS remains exploratory [132].

Focused ultrasound

MR-guided FUS with microbubbles reproducibly and reversibly opens the blood–brain barrier in AD, in hippocampus, entorhinal cortex and default-mode network targets, without serious adverse events [18,133-135]. This is a genuine technical achievement. It is not yet a therapy: a systematic review identified eight single-arm trials totalling 57 AD patients and no randomised controlled trial [136], and meta-analysis found no cognitive benefit (MMSE mean difference -0.58 , $p=0.40$) [137]. One study documented marked but reversible increases in CSF and plasma neurofilament light with unchanged A β 42/40 and p-tau181 ratios, a finding that deserves careful attention before wide adoption [135]. Combination with anti-amyloid antibodies has been reported in three patients receiving aducanumab [138]. Low-intensity transcranial FUS used as a neuromodulator (without BBB opening) has been piloted in AD [139-141]. In ALS, first-in-human BBB opening was demonstrated in four patients [142]. In PD, MRgFUS subthalamotomy improved motor scores in a randomised trial (between-group difference 8.1 MDS-UPDRS III points, $p<0.001$), but this is an ablative, motor-directed intervention, not a regenerative one, and deficits persisted at 12 months in 6 of 27 treated patients [143]; cognitive outcomes after MRgFUS thalamotomy have been assessed separately [144].

Transcranial pulse stimulation

TPS (NEUROLITH) delivers single ultrashort ultrasound pulses. Open-label and retrospective data were encouraging [145-147]. The decisive test was a randomised clinical trial of 60 AD patients, which missed its primary endpoint: the condition×session interaction on the CERAD composite was not significant ($p=0.68$, $\eta^2=0.01$), while the session main effect was significant ($p=0.007$), a pattern consistent with practice and placebo effects rather than treatment effect [148]. A subgroup aged ≤ 70 years showed benefit ($p=0.005$) and is explicitly hypothesis-generating. European CE marking was granted in 2018, before this trial. Long-term confounder analyses [149], PD data [150] and ethical commentary [151] complete the picture. TPS should not be presented to patients as an established dementia treatment.

Extracorporeal shockwave therapy

This requires an unambiguous statement. There is no published human trial of ESWT for cognition or for any neurodegenerative disease. The neurological evidence for ESWT concerns post-stroke spasticity — where randomised data are positive (for example, a 95-patient trial showing Modified Ashworth Scale reduction of 0.45, $p<0.001$) — and peripheral nerve applications [152-154]. ESWT does have real regenerative biology, including mechanotransductive activation of stem cells via Piezo1 and related channels [155], which is precisely why the extrapolation is tempting. Equating ESWT with TPS is a category error: they differ in energy density, pulse profile, focality and intended target. Clinicians in regenerative and musculoskeletal medicine, who use ESWT daily for tendinopathy, should be especially careful not to transfer that experience to the brain.

Vibration, cranial electrotherapy and hypoxic conditioning

Whole-body vibration improves cognitive measures with a small pooled effect ($g \approx 0.375$) in mixed populations, not specifically in dementia [157]. Cranial electrotherapy stimulation lacks dementia data and failed its largest randomised test [106]. Intermittent hypoxia training has a small pilot in MCI [159]; the widely cited intermittent hypoxia–hyperoxia pilot reporting cognitive and biomarker improvement has been retracted and must not be cited as evidence [160].

Synthesis by Disease

Alzheimer's disease and MCI: rTMS with network-targeted protocols and transcranial PBM currently have the strongest randomised support; tDCS has a modest effect concentrated in established AD rather than MCI; gamma sensory stimulation, gamma-tACS, TEMT, FUS and TPS have not yet produced convincing randomised primary-endpoint success (**Table 2**).

Parkinson's disease: A consistent dissociation appears: magnetic stimulation helps motor symptoms, electrical stimulation helps cognition, PBM helps neither in controlled trials, and MRgFUS is an effective but ablative motor intervention.

ALS: The evidence is thin everywhere. Cortico-spinal tDCS with a neurofilament signal and one rTMS trial with a 2.24-point ECAS gain are the only randomised positives; no gamma entrainment, PBM, PEMF or TPS trial supports use. Any claim of benefit in ALS from these devices is currently unsupported.

Vascular and mixed ("senile") dementia: Only rTMS added to cholinesterase inhibition has randomised

support; most other modalities have never been tested in this population despite it being the one most often treated commercially.

Mechanism	Modalities	Best evidence level	Key limitation
Mitochondrial/CCO activation	PBM	In vitro, animal	Biphasic dose; <10% transcranial penetration
BDNF/TrkB plasticity	tDCS, PBM, rTMS	Animal, human physiology	Genotype-dependent; not an outcome
Adult neurogenesis / NSPC expansion	tDCS, rTMS, FUS, PBM, gamma	Animal only	No human neurogenesis endpoint exists
Microglial M1→M2 and exosome release	PBM, gamma, PEMF, rotating fields	Animal, in vitro	Human biomarker data minimal
Glymphatic clearance	Gamma, FUS	Animal (AQP4-dependent)	Human amyloid PET unchanged
Mechanotransduction (Piezo1)	ESWT, FUS, vibration	In vitro, peripheral tissue	No CNS human data for ESWT

Table 1: Proposed regenerative mechanisms by modality and level of evidence.

Modality	Best design	Result	Verdict
rTMS (AD/MCI)	Meta-analysis + 2 RCTs	SMD 0.77; ADAS-Cog -5.2 (p=0.002)	Most supported; failed De Novo review
Transcranial PBM (MCI-AD)	RCT n=80	MoCA +3.87 vs -0.74 (p<0.001)	Promising, single centre
tDCS (AD)	Meta-analysis 19 RCTs	SMD 0.39 overall; 0.91 in AD; null in MCI	Modest, condition-dependent
Gamma-tACS (AD)	3 RCTs	1 positive, 2 negative	Unresolved
Gamma sensory (AD)	Meta-analysis 11 studies	SMD 0.16 (p=0.55); primary endpoints missed	Not supported to date
TEMT/PEMF (AD)	Open-label n=8	ADAS-cog p=0.09 whole group	Insufficient
FUS BBB opening (AD)	8 single-arm trials	MMSE MD -0.58 (p=0.40)	No cognitive benefit shown
TPS (AD)	RCT n=60	Primary endpoint missed (p=0.68)	Not supported
ESWT (any neurodegenerative disease)	None	No human trial	No evidence

Table 2: Best controlled clinical evidence by modality (cognitive outcomes).

Limitations, Safety and a Research Agenda

Limitations of this review: It is narrative, single-author and unregistered; study selection was expert-guided rather than exhaustive, and no formal risk-of-bias instrument or quantitative pooling was applied. Publication bias almost certainly inflates the positive literature in every modality reviewed, as the discordance between meta-analytic effect sizes and regulatory trial outcomes illustrates.

Safety: The safety record is genuinely reassuring. No serious adverse events were reported across more than 18,000 transcranial electrical stimulation sessions and more than 33,200 tDCS sessions in systematic safety reviews [120]. rTMS seizure risk is quantified and manageable under published guidelines [122]. PBM tolerability is dose-dependent and favourable [80]. Notable exceptions: increased tinnitus with gamma auditory stimulation [40] and reversible neurofilament elevations after FUS BBB opening [135]. Safety, however, is not efficacy, and low risk can rationalise indefinite use of ineffective therapy at real financial and opportunity cost.

What the field needs: (i) Adequately powered, multicentre, sham-controlled trials with pre-registered primary cognitive endpoints and blinding validity checks — the last are almost universally absent. (ii) Dosimetry standardisation: reported fluence at the cortex, not at the device aperture; field strength at

target; acoustic pressure at focus (iii) Mechanistic endpoints that bridge to regenerative medicine — plasma and CSF BDNF, p-tau217, neurofilament light, glymphatic MRI, microglial PET and, where feasible, exosomal cargo profiling. (iv) Head-to-head and combination designs, including device plus anti-amyloid antibody, device plus MSC or exosome therapy, and device plus structured exercise. (v) Disease-specific trials in ALS and vascular dementia rather than extrapolation from AD. (vi) Transparent reporting of negative and failed-replication results.

Conclusion

Physical, device-based neuromodulation occupies a genuine and mechanistically coherent place within regenerative neuroscience: photons, currents, magnetic flux and acoustic pressure demonstrably modulate mitochondrial function, neurotrophin signalling, microglial phenotype, exosomal signalling, glymphatic clearance and adult neural stem/progenitor cell dynamics. That biology is real and is worth pursuing seriously.

The clinical reality is more sober. Only repetitive transcranial magnetic stimulation, and possibly transcranial photobiomodulation, currently rest on replicated randomised evidence of cognitive benefit, and even rTMS failed a formal regulatory efficacy review. Gamma sensory stimulation, transcranial pulse stimulation, transcranial electromagnetic treatment and focused ultrasound have each generated headlines out of proportion to their primary-endpoint results, and extracorporeal shockwave therapy has no human evidence in neurodegenerative disease at all. Two influential papers in this space have been retracted.

For clinicians in regenerative medicine the appropriate position is neither dismissal nor advocacy. These are low-risk, biologically interesting interventions that should be offered, when offered at all, within trials or with explicit disclosure of their investigational status, honest presentation of what the primary endpoints actually showed, and a clear distinction between a device that has been designated, cleared or CE-marked and one that has been proven to work. The next five years — with a pivotal gamma trial reading out in 2026 and multicentre PBM and tACS studies under way — will determine whether this field matures into validated regenerative neurotherapeutics or remains an elegant mechanism in search of a clinical effect.

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Conflict of interest

The author declares no conflict of interest. The author has no financial or commercial relationship with any manufacturer of the devices discussed.

Ethics approval and consent to participate

Not applicable. This article is a review of previously published literature and did not involve human participants, human tissue, identifiable personal data or animal experimentation; institutional review board / research ethics committee approval and informed consent were therefore not required.

Data availability

All data discussed are available in the cited published literature and in the public registries and regulatory documents referenced.

Use of artificial intelligence

Artificial-intelligence tools were used to assist with literature retrieval, reference formatting and language editing. All scientific content, interpretation, critical appraisal and conclusions are the author's own, and all cited sources were verified against their primary records by the author. No AI-generated images were used.

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