Therapeutic noninvasive brain stimulation in Alzheimer's disease and related dementias

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Purpose of review
Alzheimer's disease is a progressive neurodegenerative disease without effective pharmacological treatment. Noninvasive brain stimulation (NIBS) techniques, such as repetitive transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES), are increasingly being investigated for their potential to ameliorate the symptoms of Alzheimer's disease and related dementias (ADRD).

Recent findings
A comprehensive literature review for primary research reports that investigated the ability of TMS/tES to improve cognition in ADRD patients yielded a total of 20 reports since 2016. Eight studies used repetitive TMS and 12 used transcranial direct current stimulation, the most common form of tES. Eight of the studies combined NIBS with cognitive training. Promising results should encourage continued investigation, however there is currently insufficient evidence to support widespread adoption of NIBS-based clinical treatments for ADRD.

Summary
NIBS remains an active area of investigation for treatment of ADRD, though the predominance of small, heterogeneous, proof-of-principle studies precludes definitive conclusions. We propose the establishment of a consortium to achieve the benefits of large-scale, controlled studies using biomarker-based diagnostic characterization of participants, development of neurophysiological markers to verify target engagement, and standardization of parameters.

Keywords
Alzheimer's disease, mild cognitive impairment, noninvasive brain stimulation, repetitive transcranial magnetic stimulation, transcranial electrical stimulation

INTRODUCTION

Alzheimer's disease is the most common cause of dementia worldwide [1]. With the growth of the aging population, the prevalence of Alzheimer's disease in the United States alone is projected to rise from 5.5 to 13.8 million by 2050 unless new treatments to prevent, slow, or reverse the disease are developed [2]. Currently available medications for Alzheimer's disease may offer some symptomatic relief [3,4], but do not alter the underlying disease process or pathology. Recent drug trial failures for Alzheimer's disease and related dementias (ADRD) have left the field with a lack of disease-modifying therapies [5,6]. In this context, nonpharmacological interventions including lifestyle modifications, physical activity, cognitive training, and noninvasive brain stimulation (NIBS) have been increasingly investigated as potential treatments or symptomatic therapies for Alzheimer's disease -related cognitive decline [7–10]. This review will focus on the two most widely studied NIBS techniques to-date, transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). However, we want to emphasize that given the complex pathophysiologic nature of ADRD, a single therapeutic intervention is unlikely to be a satisfactory response, and that combination of various interventions is probably critical. NIBS has the appeal that can be easily combined with pharmacologic and

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KEY POINTS

- NIBS with or without cognitive training has the potential to improve cognition in ADRD.
- A paucity of large-scale trials and a lack of consistency in treatment parameters precludes definitive conclusions.
- The use of available biomarkers would greatly improve diagnostic characterization of ADRD patients.
- Neurophysiological or modeling-based indicators are needed to confirm the engagement of cortical targets and monitor stimulation efficacy.
- The field would benefit from a consortium or other multisite coordinated efforts.

behavioral interventions, and may play a useful role in future multimodality treatment approaches that are likely to be needed in ADRD.

TMS is a means of inducing brief pulses of intracranial electrical currents with a powerful, rapidly fluctuating, handheld electromagnet [11]. A single pulse of TMS can depolarize neuronal membranes leading to action potentials. TMS of the primary motor cortex can evoke descending corticospinal volleys, which can give rise to activations of contralateral muscles. These can be recorded as motor evoked potentials via electromyography. TMS to motor or nonmotor regions can also elicit intracranial TMS-evoked potentials that can be recorded via electroencephalography and are presumed to be the results of activation of cortical neural elements. Delivering trains of TMS pulses at a specified frequency and intensity, termed repetitive TMS (rTMS), can induce changes in brain excitability that can persist for some time after the period of stimulation [12]. The immediate aftereffects of a single rTMS application are typically measured as changes in the performance of a behavioral task or some measure of cortical excitability, such as the average amplitude of motor evoked potentials or TMS-evoked potentials. Daily sessions of rTMS are thought to yield a cumulative effect and form the basis for the stimulation protocols used with devices cleared by the US Food and Drug Administration for clinical treatment of patients with medication-resistant major depression [13] and obsessive-compulsive disorder [14].

In ADRD, several small pilot studies have shown promise using rTMS protocols to improve global cognition or language function [15–17], either using rTMS alone or combined with cognitive training. One example is the NeuroAD protocol (Neuronix Ltd., Yoqneam, Israel), in which rTMS is delivered to six brain regions and paired with interleaved cognitive training of the function associated with the targeted brain region [18]. There have been several early proof-of-principle studies using the NeuroAD protocol [15,16]. In 2016, a large multisite clinical trial (ClinicalTrials.gov: NCT01825330) was completed and awaits a final declaration by the US Food and Drug Administration.

The other major form of NIBS is tES, which involves passing weak electrical current between two or more electrodes placed on the scalp [19,20]. The most common form of tES is transcranial direct current stimulation (tDCS), in which a constant current (typically 1–2 mA) is applied to create electrical gradients, which are thought to modulate cortical excitability indirectly by increasing (depolarizing) or decreasing (hyperpolarizing) the resting membrane potentials of neural elements in the vicinity of the anode or the cathode, respectively [21,22].

In ADRD, tDCS has been studied as a therapeutic tool in several pilot studies, and has shown promise in improving memory performance [23–25]. Other forms of tES include transcranial alternating current stimulation (tACS), in which the current is rapidly alternated at a specific frequency to entrain cortical oscillations, and transcranial random noise stimulation (tRNS), in which a full-band current spectrum is applied to boost endogenous rhythms by means of stochastic resonance [26]. Although there have not been many studies using tACS in ADRD to date, it is an appealing approach given evidence of abnormal brain oscillations in Alzheimer's disease [27]. Similarly, although there have not been any published reports investigating the potential therapeutic benefit of tRNS in ADRD, it has been shown to improve fluid intelligence in healthy adults when paired with adaptive cognitive training [28]. Future studies may explore the potential of these and other new NIBS techniques for ADRD.

The purpose of the present review is to assess recent developments in the investigation of NIBS as treatment for ADRD. Although preliminary studies of TMS and tDCS have shown evidence of improving specific cognitive domains Alzheimer's disease, there is at present no clear consensus about which NIBS paradigms are the most promising for treatment of ADRD, and which, if any, might be disease-modifying vs. simply symptomatic. Given the rapidly changing state of the field, this review includes only recent studies from 2016 to 2018 and focuses on those investigations into the clinical benefit of NIBS to treat Alzheimer's disease. For state of the field before 2016, we refer to a prior review by Gonsalvez *et al.* [7]. Since 2016, there have been a number of studies investigating the diagnostic

[29,30] or prognostic [31] potential of NIBS for ADRD, or to better understand its pathophysiology [32,33], but these are outside the scope of this review. We will discuss commonalities and discrepancies across interventional studies and point out areas where further investigation is needed. Finally, we will discuss future directions, including opportunities offered by novel technologies in NIBS.

METHODS

A literature search was performed in PubMed using the following Boolean combinations of terms related to ADRD ('Alzheimer's,' 'mild cognitive impairment (MCI),' 'dementia') and those related to NIBS ('noninvasive brain stimulation,' 'noninvasive brain stimulation,' 'TMS,' 'rTMS,' 'theta burst stimulation,' 'transcranial electrical stimulation,' 'transcranial current stimulation,' 'tDCS,' ' tACS,' and 'tRNS'). Articles with a publication date prior to 1 January 2016 were excluded as they were reviewed and discussed in Gonsalvez *et al.* [7]. Abstracts were reviewed and selected for inclusion if they represented a case study, case series, pilot or proof-of-principle study, or randomized control study for the use of NIBS as a treatment for Alzheimer's disease or MCI, with a primary aim of improving cognitive function. Studies focusing primarily on other disease pathologies or other diagnostic groupings were not included.

RESULTS

Figure 1 shows a flow diagram of the PubMed search. The literature search yielded 39 studies focused on treatment of neurodegenerative disorders using NIBS techniques from 2016 to 2018; 20 of these focused on the treatment of cognition in Alzheimer's disease or MCI were included in this review. The additional 19 studies investigated NIBS treatments for other neurodegenerative pathologies, and included primary progressive aphasia, frontotemporal dementia, MCI because of Parkinson's disease, Lewy body disease, and other conditions outside of the scope of the current review.

Trials using repetitive transcranial magnetic stimulation in Alzheimer's disease and related dementias

Table 1 lists the eight articles focusing on rTMS treatment of Alzheimer's disease that were included in the review. Six of the eight studies focused on patients meeting criteria for Alzheimer's disease dementia [34▪,35▪▪,36,37▪,38▪,39▪], whereas two studies focused on early-stage Alzheimer's disease (prodromal Alzheimer's disease or MCI) [40▪▪,41▪]. Determination of MCI or Alzheimer's disease status was primarily based on clinical diagnostic criteria with one study used cerebral spinal fluid (CSF) biomarkers to confirm the diagnosis [40▪▪].

Parameters of rTMS stimulation (including intensity, frequency, duration, and number of

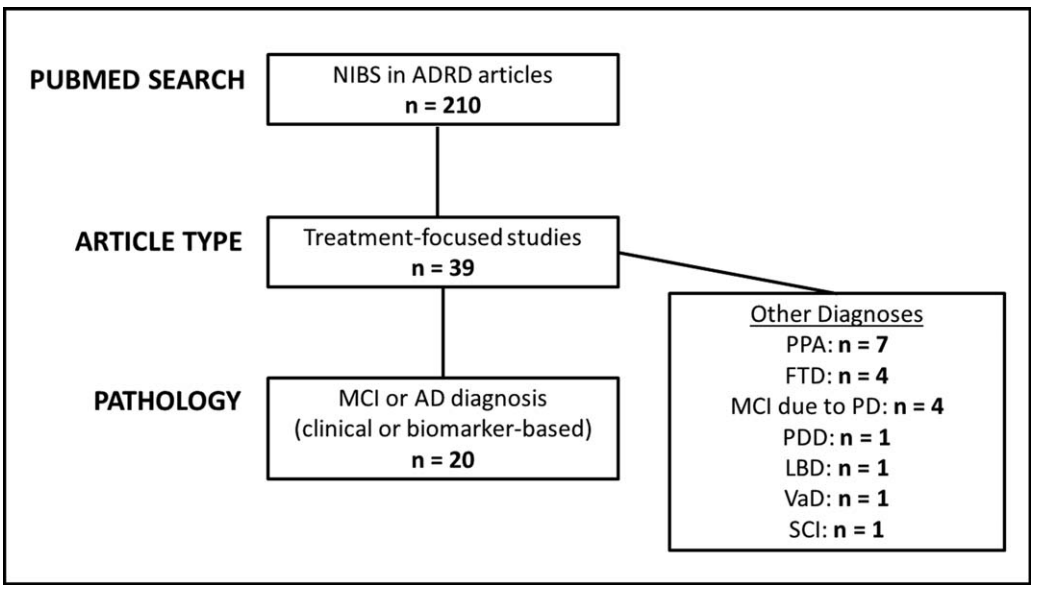

FIGURE 1. Investigations of NIBS for treatment of ADRD since 2016. Flow diagram of literature search. AD, Alzheimer's disease; FTD, frontotemporal dementia; LBD, Lewy body disease; MCI, mild cognitive impairment; NIBS, noninvasive brain stimulation; PD, Parkinson's disease; PDD, Parkinson's disease dementia; PPA, primary progressive aphasia; SCI, subjective cognitive impairment; VaD, vascular dementia.

Table 1. Studies investigating transcranial magnetic stimulation as a therapeutic tool in ADRD

TMS studies 2016–2018 (references)	Criteria for AD/MCI (disease stage)	No. of participants	Sham/ control	Age (mean ± SD)	Target area; localization method	Interleaved cognitive training	Intensity (% RMT)	TMS frequency and pattern	Stimulation duration; number of TMS trains; number of pulses/day	Length of intervention; iumber of sessions	Cognitive domain	Neuropsychological tests – primary outcome	Neuropsychological tests – secondary outcomes	Main sgnificant neuropsychological findings
Pilot studies and RCTs														
[35▪▪]	Probable AD based on DSM-IV criteria, CDR 1–2, MMSE 18–26 (mild–moderate AD)	26	2:1 treatment: sham	Treatment group age = 71.2 ± 7.6, sham group age = 70.3 ± 4.8	Six brain regions; MRI guided	Yes	90–110% RMT	10 Hz rTMS; 20 trains applied with 2 s on, 20–40 s off; with interleaved cognitive task	1 h session/day; three brain regions/day; 1200 pulses/day	6 weeks; 30 sessions	Global cognition	ADAS-Cog	MMSE; CGIC; GDS	There was a significant improvement after the intervention in ADAS-Cog in the treatment group, but the between-group difference compared with sham was not significant. In both treatment and sham, the largest improvement was seen in mild AD compared to moderate AD
[36]	Probable AD based on DSM-IV criteria, CDR 1–2, MMSE 18–26 (mild–moderate AD)	30	17:13 treatment: sham	Treatment group age = 69.3 ± 5.8, sham group age = 71.4 ± 5.2	Treatment areas not clearly specified, but included parietal P3/P4, posterior temporal T5/T6; 10–20 system	Yes	Not specified	20 Hz rTMS; 20 trains applied with 10 s on, 20 s off; with interleaved cognitive tasks	1 h session/day; 3 brain regions/ day; not specified	6 weeks; 30 sessions	Global cognition and verbal memory	Not specified	ADAS-Cog, MMSE, MOCA, AVLT	There was a significant improvement in ADAS-Cog, MMSE, and AVLT in the treatment group, but there was no between-group difference compared with sham. Mild AD showed a larger improvement compared with moderate AD
[34▪]	Probable AD by clinical diagnosis, severity ranging from MCI to moderate-to-severe AD	10	None	Age = 70.3 (7.2)	Six brain areas and L DLPFC and R DLPFC; MRI guided	Yes	100% RMT	Six brain region treatment: 10 Hz rTMS; 20 trains applied with 2 s on over 10 min; with interleaved cognitive training. DLPFC treatment: 10 Hz rTMS; 5 trains applied with 2 s on over 2.5 min; with interleaved cognitive training	1 h session/day; four brain regions/day; up to 1300 pulses/ day	5 weeks; 25 sessions	Global cognition	ADAS-Cog	Preformance on interleaved cognitive training tasks, MMSE, DuBios score, FAB, Stroop test, locomotor score, apathy score, caregiver burden interview, dependence score	Immediately after the treatment procedure, there was improvement in the ADAS-Cog, locomotor score, apathy score, and dependence score. Six months later, ADAS-Cog scores had returned to baseline, but apathy and dependence scores continued to show improvement
[40▪▪]	Prodromal AD by Dubois, 2016 criteria with positive CSF biomarker	14	Crossover design, with participants receiving both treatment and sham stimulation	Age = 70.0 ± 5.1	Precuneus; MRI guided, stimulation site confirmed with source localization	No	100% RMT	20 Hz rTMS; 40 trains applied with 2 s on, 28 s off	20 min of rTMS; 1600 pulses/day	2 weeks; 10 sessions	Verbal memory, EEG, and TMS-EEG	Not specified	RAVLT, MMSE, FAB, DSST	RAVLT delayed recall showed a significant improvement after treatment compared with sham; other tests showed no main effect of treatment

Table 1 (*Continued*)

TMS studies 2016–2018 (references)	Criteria for AD/MCI (disease stage)	No. of participants	Sham/ control	Age (mean ± SD)	Target area; localization method	Interleaved cognitive training	Intensity (% RMT)	TMS frequency and pattern	Stimulation duration; number of TMS trains; number of pulses/day	Length of intervention; iumber of sessions	Cognitive domain	Neuropsychological tests – primary outcome	Neuropsychological tests – secondary outcomes	Main sgnificant neuropsychological findings
[37▪]	Diagnosis of AD by DSM-V, MMSE ≥ 15, GDS-Reisberg level 2–4	19	1:1 randomization into two active treatment groups: 'simple' vs. 'complex' stimulation protocol	Simple group age = 73.3 ± 6.0; complex group age = 71 ± 4.3	Simple protocol: single-site DLPFC stimulation. Complex protocol: six brain regions; 10–20 system	No	100% RMT	5 Hz rTMS; 30 trains applied with 10 s off, 60 s off	In the Simple Protocol, 3 single-site stimulation was applied to DLPFC daily, in the Complex Protocol, 3 brain regions were treated daily; 1500 pulses/day	3 weeks; 15 sessions	Global cognition	ADAS-Cog	MMSE, NPI, GDS, IDDD, CGI	Both treatment groups showed an improvement in ADAS-Cog, MMSE, IDDD, NPI immediately after treatment, which persisted one month later. There was no significant difference between the two treatment groups
[41▪]	MCI diagnosis by Peterson's criteria, MMSE ≥23, with apathy (AES-C ≥30).	8	Double-blind, randomized, crossover design, with participants receiving both treatment and sham	Group 1 age = 68.0 ± 10.0; Group 2 age = 64.0 ± 9.0	L DLPFC; 5.5 cm anterior to motor hotspot location	No	120% RMT	10 Hz rTMS; 75 trains applied with 3 s on, 26 s off	37.5 min of rTMS; 3000 pulses/day	2 weeks; 10 sessions	Apathy	AES-C	3MS, MMSE, TMT B, TMT A, EXIT-25, CGI, I-ADLS, ADLS, ZBS	There was a significant improvement in AES-C after the active treatment compared to the sham condition. There was also significant improvement in 3MS, MMSE, TMT A, and CGI-I in the treatment group compared with sham
Case reports and clinical case series														
[38▪]	Moderate–severe AD by clinical diagnosis	11	None	Age = 76 ± 7	Bilateral prefrontal cortex using deep TMS; 6 cm anterior to motor hotspot location	No	120% RMT	10 Hz deep TMS, 42 trains applied with 2 s on, 20 s off	One 20-min session/day, 2–3 times per week, with a minimum interval of 1 day between sessions	20 sessions	Global cognition	n/a	Mindstreams and ACE	60% of patients improved on Mindstreams, and 77% showed improvement on the ACE compared to baseline. Treatment with dTMS significantly improved ACE scores in a subset of the most progressed patients
[39▪]	Mild-to-moderate AD clinical diagnosis	30	None; patients treated in two private clinics offering commercial NeuroAD treatments	Not reported	Six brain regions; MRI guided	Yes	90–110% RMT	3/4 paradigms: 10 Hz rTMS; 20 trains applied with 2 s on over 10 min; with interleaved cognitive training. 1/4 Paradigm: 10 Hz rTMS; 5 trains applied with 2 s on over 2.5 min; with interleaved cognitive training	1 h session/day; three brain regions/day; 1300 pulses/day	6 weeks; 30 sessions	Global cognition	n/a	ADAS-Cog and MMSE	ADAS-Cog and MMSE both improved posttreatment compared to baseline scores

Studies investigating TMS for treatment of ADRD using clinical or biomarker diagnostic criteria. Age is shown as mean ± SD or mean (SEM). Several studies followed the NeuroAD protocol, targeting six brain regions: R prefrontal, L prefrontal, R parietal, L parietal, Broca's area, and Wernicke's area.

AD, Alzheimer's disease; 3MS, Modified Mini-Mental Status Examination; ACE, Addenbrooke Cognitive Examination; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive; ADLs, activities of daily living; ADRD, Alzheimer's disease and related dementias; AES, Apathy Evaluation Scale; AVLT, Auditory-Verbal Learning Test; BDS, Blessed Dementia Scale; CGI, Clinical Global Impression; CGIC, Clinical Global Impression of Change; DLPFC, dorsolateral prefrontal cortex; DSST, Digit Symbol Substitution Test; dTMS, deep TMS; EXIT-25, Executive Interview; DSM IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; FAB, frontal assessment battery; GDS, Geriatric Depression Scale; I-ADLS, instrumental activities of daily living; IDDD, Interview for Deterioration in Daily Living Activities in Dementia; L DLPFC, left dorsolateral prefrontal cortex; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; RAVLT, rey auditory verbal learning test; RMT, resting motor threshold; TMS, transcranial magnetic stimulation; TMT, Trail Making Test; TMT A, trail making test, part-A; TMT B, trail making test, part-B; ZBS, Zarit Burden Scale.

sessions) varied considerable across protocols. Half of the studies used MRI-guided neuronavigation [34▪,35▪▪,39▪,40▪▪]. Brain regions targeted included the precuneus, prefrontal cortex, and a multisite 6-ROI protocol adapted from NeuroAD. Interleaved cognitive training was included in four of the rTMS studies following the NeuroAD approach [34▪,35▪▪,36,39▪]. Two studies employed a sham control [35▪▪,36], two studies employed a crossover design with participants receiving both sham and treatment conditions sequentially [40▪▪,41▪], and one study compared two different stimulation paradigms [37▪].

The primary cognitive outcome measures studied included global cognition, verbal memory, and apathy. Overall, results suggested a potential for improvement in cognitive measures after rTMS treatments, but results were mixed as to whether rTMS was significantly more effective than sham.

Trials using transcranial electrical stimulation in Alzheimer's disease and related dementias

Table 2 lists the 12 trials using tES as a treatment in Alzheimer's disease that were included in the review. Alzheimer's disease and MCI diagnoses were mostly made clinically [42▪▪,43▪,44▪▪,45▪,46,47▪▪, 48,49,50▪,51▪,52▪], aside from one case report of posterior cortical atrophy [53▪] which confirmed Alzheimer's disease biomarker positivity using CSF. Five studies focused on MCI [43▪,44▪▪, 45▪,46,47▪▪]. One case series examined the use of tES for treatment of auditory hallucinations in Alzheimer's disease and Lewy body disease [51▪], and another case report examined tES for treatment of language dysfunction in Alzheimer's disease [52▪].

Most tDCS studies applied stimulation to patients while they were awake, but one study examined slow oscillatory tDCS delivered during a daytime nap [44▪▪]. Four of the tDCS studies included cognitive training either before or during brain stimulation, with the intent to use brain stimulation to potentiate the effects of task-specific learning [46,47▪▪,52▪,53▪]. Out of 12 studies, three employed a separate sham control [42▪▪,43▪,47▪▪], and three employed sham in a crossover design [44▪▪,46,52▪]. Electrode localization exclusively used scalp landmarks; no studies used neuronavigation or modeling to target stimulation. Brain regions targeted included either bilateral or unilateral prefrontal cortex or temporal lobe.

A variety of neuropsychiatric outcomes were measured across studies, including global cognition, verbal memory, visual memory, subjective memory, and language. Overall, results suggested a potential for boosting cognitive function using tES, but results were mixed as to whether tES demonstrated statistically significantly superiority compared to sham.

DISCUSSION

This review found an ongoing, robust interest in the application of NIBS to ADRD, spanning a range of disease severity. Since our previous review capturing data until 2016 [7], there have been 12 new randomized-controlled trials or proof-of-principle studies, and 8 new case reports or clinical case series, representing a combined 244 ADRD patients studied. Results were encouraging for the use of NIBS to improve global cognition and memory measures in patients with a clinical diagnosis of Alzheimer's disease. However, widespread adoption of NIBS as a standard course of treatment remains hindered by a number of methodological challenges, including the lack of clear consensus regarding optimal stimulation parameters, with variability seen in the type, intensity, frequency, location, and duration of stimulation. In the future, studies with larger numbers of participants, rigorous blinding and sham procedures, and biomarker-confirmation of Alzheimer's disease diagnosis are needed to validate whether NIBS techniques are useful as primary or adjunct treatments for ADRD. In the following paragraphs, we summarize and discuss the strengths and limitations of the state-of-the-field in several key areas.

Patient characterization

Great strides have been made in developing *in vivo* biomarkers of Alzheimer's disease pathophysiology, chiefly, tests for β-amyloid and tau proteins in the CSF or on positron emission tomography imaging. The recent National Institute of Aging – Alzheimer's Association (NIA-AA) research framework proposed by Jack *et al.* [54] promotes a biomarker-based definition of Alzheimer's disease *in vivo*, allowing for standardization of diagnostic criteria for use in interventional research and biomarker studies. Whether because of cost, risk, limited access, or a combination of these factors, only a few studies in our review confirmed Alzheimer's disease pathology using available biomarkers, and none demonstrated alteration of underlying disease pathogenesis. Instead, most studied relied on probable diagnostic criteria based on clinical and neuropsychological evaluations. The lack of thorough characterization of patients invites unknown heterogeneity, which in turn increases the risk of Type II (or false-negative) errors. Improvements in diagnostic characterization of patients will also facilitate the search for interventions for different variants of Alzheimer's disease, dementias of non-Alzheimer's disease

Table 2. Studies investigating transcranial electrical stimulation as a therapeutic tool in ADRD

Electrical stimulation studies 2016-2018 (references)	Criteria for AD/MCI (disease stage)	No. of partici-pants	Type of stimulation	Sham/ control	Interleaved cognitive stimulation	Age (mean ± SD)	Target area; localization method	Scalp electrode 1	Scalp electrode 2	Scalp electrode size (cm^2)	Extracranial electrode and size (cm^2)	Current	Duration (min)	Total number of sessions; length of intervention	Cognitive domain	Neuropsycho-logical tests – primary outcome	Neuropsy-chological tests – secondary outcomes	Main significant neuropsycho-logical findings
Pilot studies and RCTs																		
[42▪▪]	Probable AD with increased level of certainty by NINCDS-ADRDA; MMSE >18	25	tDCS; awake	1:1 treatment: sham	No	Treatment group age= 70.0±8.0; sham group age=75.0±8.7	L temporal lobe; 10-20 system	Anode= T3	Cathode = Fp2	35	None	2 mA	30	Six sessions; 10 days	Verbal memory	CVLT-II	MMSE, TMT A, TMT B, clock-drawing test	No significant differences in CVLT-II, MMSE, TMT A, TMT B, or clock drawing test were seen between the treatment and sham group
[43▪]	MCI diagnosis by Peterson criteria	16	tDCS; awake	1:1 treatment: sham	No	Treatment group age = 74.8±7.5; sham group age = 73.1 ±4.2	Bilateral DLPFC; 10–20 system	Anode=F3	Cathode = F4	25	None	2 mA	30	Nine sessions; 3 weeks	Subjective Memory Complaint Scale from participants, FDG-PET	MMQ	n/a	The treatment group showed improvement in subjective memory scores on the MMQ-A (ability) and MMQ-C (contentment) subscores compared to sham
[44▪▪]	Amnestic MCI (single or multidomain) by mayo criteria, with objective cognitive decline with scores <1 SD below norms on memory tests; MMSE ≥24	16	Slow oscillatory tDCS; delivered during a daytime nap	Balanced crossover design, each participant received one treatment and one sham session, at least 2 weeks apart	No	Age=71±9	Bifrontal stimulation, using anodal current with sinusoidal oscillations at a frequency of 0.75 Hz; 10–20 system	F3	F4	0.64	Bilateral mastoids; 0.64	0.522 mA/cm2…	15–25 (5 min blocks of stimulation given during stage 2,3, or 4 NREM sleep, for a total of 3–5 blocks)	One session; 1 day	Visual recognition memory, EEG	Visuospatial memory task comprised on neutral pictures taken from the International Affective Picture System	Procedural finger-tapping task, verbal memory task, location memory task	There was an improvement in visual recognition memory in the treatment group compared to sham when controlling for sleepiness. There was no effect of treatment on procedural memory, verbal memory, or location memory
[45▪]	MCI diagnosis by NIA-AA criteria, CDR=0.5	11	tDCS; awake	None	No	Age=59.6	L DLPFC; 10–20 system	Anode= F3-FP1	Cathode = R supra-orbital region	35	None	2 mA	20	Five sessions; 5 days	Visual memory	PMIT	n/a	Improved immediate and delayed recall on the PMIT immediately after conclusion of the treatment. Improvement on delayed recall PMIT persisted 1 month later

Table 2 (*Continued*)

Electrical stimulation studies 2016-2018 (references)	Criteria for AD/MCI (disease stage)	No. of partici-pants	Type of stimulation	Sham/ control	Interleaved cognitive stimulation	Age (mean ± SD)	Target area; localization method	Scalp electrode 1	Scalp electrode 2	Scalp electrode size (cm^2)	Extracranial electrode and size (cm^2)	Current	Duration (min)	Total number of sessions; length of intervention	Cognitive domain	Neuropsycho-logical tests – primary outcome	Neuropsy-chological tests – secondary outcomes	Main significant neuropsycho-logical findings
[46]	MCI diagnosis by modified Peterson's criteria, MOCA 19–26, CDR ≤0.5	5	tDCS; awake	A-B-C-A protocol; anodal tDCS + CS, sham tDCS + CS, and CS only	Yes	Age = 72.8 ± 6.6	L DLPFC; 10–20 system	Anode = L DLPFC	n/a	35	R deltoid; 35	2 mA	30	One to five sessions total of active tDCS + cognitive stimulation	Not specified	Not specified	Preformance on cognitive stimulation tasks from neuron Up, MOCA, digit span, TMT	Some participants showed improvement on several measures, but no statistically significant conclusions can be drawn
[47▪▪]	Amnestic MCI by Peterson criteria, MMSE 24–30, CDR = 0.5	18	tDCS; awake	1:1 treatment: sham	Yes	Treatment group age = 75.3 ± 4.8; sham group age=75.3 ±2.2	L lateral prefrontal cortex; 10–20 system	Anode = F3	Cathode = Fp2	35	n/a	1.5 mA	15	Day 1 = initial learning session only, day 2 = memory reactivation + active tDCS or sham session, day 3 and day 30 = retrieval session only	Verbal memory	Experimental memory task (learning, reactivation, free recall, and recognition)	n/a	Active tDCS treatment enhanced Memory Recognition scores compared to sham
Case reports and clinical case series																		
[48]	AD diagnosis by NINCDS-ADRDA criteria, CDR = 1	1	tDCS; awake	None	No	Age = 73	L DLPFC; 10–20 system	Anode = F3	Cathode = R supraorbital region	35	n/a	2 mA	30	10 sessions; 2 weeks	Global cognition	ADAS-Cog	NPI, BDS, DAD	After treatment, ADAS-Cog, NPI, BDS, and DAD showed improvement compared to baseline
[49]	Early AD diagnosis, 1 criteria not specified		tDCS; awake	None	No	Age = 59	L temporal lobe; 10–20 system	Anode = T3	Cathode = FP2	Not specified	n/a	2 mA	30	12 sessions; 6 days	Verbal memory	CVLT-II, EEG	MMSE, TMT A, D-KEFS Word Fluency, WMS Attention span, clock-drawing test	After treatment, the CVLT-II and MMSE showed improvement compared to baseline
[50▪]	Early-onset AD, Dubois criteria	1	tDCS; awake, applied at home with help from family	None	No	Age = 60	L temporal lobe; 10–20 system	Anode = T3	Cathode = FP2	Not specified	n/a	2 mA	30	Daily for 8 months	Memory, visuospatial, language, and attention	RBANS		Overall the patient's cognitive function remained stable over 8 months, with improvement in memory (immediate and delayed recall), and decline in visuospatial function

Table 2 (*Continued*)

Electrical stimulation studies 2016-2018 (references)	Criteria for AD/MCI (disease stage)	No. of partici-pants	Type of stimulation	Sham/ control	Interleaved cognitive stimulation	Age (mean ± SD)	Target area; localization method	Scalp electrode 1	Scalp electrode 2	Scalp electrode size (cm^2)	Extracranial electrode and size (cm^2)	Current	Duration (min)	Total number of sessions; length of intervention	Cognitive domain	Neuropsycho-logical tests – primary outcome	Neuropsy-chological tests – secondary outcomes	Main significant neuropsycho-logical findings
[52▪]	Possible AD diagnosis by NINCDS-ADRDA criteria, MMSE = 14.27	1	tDCS; awake	One week of sham was followed by treatment intervention	Yes	Age = 67	R angular and supramarginal gyrus; 10–20 system	Anode = P6-CP6	Cathode = L supraorbital region	35	n/a	2 mA	30	five sessions; 1 week	Language	BADA		After treatment there was a significant improvement in comprehension of verbs, compared to sham. This persisted for 2 weeks poststimulation.
[53▪]	Posterior cortical atrophy with AD diagnosis via CSF tau and α-β	1	tDCS; awake	None	Cognitive rehab therapy preformed prior to initiation of tDCS	Age = 58	L DLPFC; 10–20 system	Anode = F3	n/a	Not specified	R shoulder	2 mA	20	20 sessions; 4 weeks; repeated for two separate cycles, total of 40 tDCS sessions	Executive function, fMRI	Stroop task while in the fMRI scanner	Complete NPS evaluation	The patient showed improvement on the Stroop task after cognitive training, which was maintained after the first and second tDCS cycle
[51▪]	One patient with an AD diagnosis, one patient with a LBD diagnosis	2	High definition tDCS; awake	None	No	AD patient age =; LBD patient age = 68	10–10 system	High definition tDCS used five ring electrodes arranged on the scalp around the central Cathode	Cathode = CP5	Ring electrodes with outer radius 12 mm, inner radius 6 mm	n/a	2 mA	20	Two sessions per day, 10–20 sessions total; 5–10 days of treatment	Auditory hallucinations	AHRS		Both the AD and LBD patient showed decrease frequency of auditory hallucinations on the AHRS and decreased acting out behavior

Studies investigating tES for treatment of Alzheimer's disease and related dementias using clinical or biomarker diagnostic criteria. Age is shown as mean ± SD.

AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive; AHRS, Auditory Hallucinations Rating Scale; BADA, Battery for the Analysis of the Aphasic Deficit; BDS, Blessed Dementia Scale; CDR, clinical dementia rating; CVLT, California Verbal Learning Test; CSF, cerebral spinal fluid; DAD, Disability Assessment for Dementia; D-KEFS, Delis-Kaplan Executive Function System; DLPFC, dorsolateral prefrontal cortex; FDG-PET, fluorodeoxyglucose positron emission tomography; EEG, electroencephalography; LBD, Lewy body dementia; L DLPFC, left dorsolateral prefrontal cortex; MCI, mild cognitive impairment; MMQ, Multifactorial Memory Questionnaire; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; NIA-AA, National Institute of Aging – Alzheimer's Association; NINCDS, National Institute of Neurological and Communicative Disorders and Stroke; NPI, Neuropsychiatric Inventory; NREM, non-rapid eye movement; PMIT, Picture Memory Impairment Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RCTs, randomized controlled trials; tDCS, transcranial direct current stimulation; tES, transcranial electrical stimulation; TMT, Trail Making Test; TMT A, trail making test, part-A; TMT B, trail making test, part-B; WMS, Wechsler Memory Scale.

etiologies, and preclinical/prodromal populations (for recent meta-analyses, see [55,56]). Attempts have been made to improve information about and access to Alzheimer's disease biomarker test, including the recently completed Imaging Dementia – Evidence for Amyloid Scanning study (ClinicalTrials.gov: NCT02420756). In the future, we recommend a biomarker-based approach to study participant inclusion in NIBS treatment trials, to confirm disease pathology and assure translatability to clinical populations.

Study design and use of sham/placebo

Small pilot studies were the most common encountered in the literature, followed by clinical reports. Publications of large, randomized, double-blinded, placebo-controlled clinical trials were lacking. The majority of studies approached NIBS as a symptomatic treatment, aimed at boosting specific domains of cognitive function. More than a third of studies employed interleaved cognitive training or used NIBS to boost or extend the effects of previously performed cognitive rehabilitation.

Our review found no large-scale studies demonstrating superiority of NIBS treatments compared to sham stimulation. Recently, there has been a resurgence of interest in the placebo effect and its implications for clinical research (for a review, see [57]). This is particularly relevant to NIBS, in which appropriate blinding is difficult to obtain because of the occurrence of robust peripheral (auditory, somatosensory, and motor) effects that accompany TMS pulses or the ramping of tES currents. Cross-over designs offer additional challenges given potential carry-over and long-lasting effects, as well as intra-individual variability of NIBS [58] coupled with interindividual or disease-specific differences in expectation and memory, which can result in effects that are difficult to interpret. These challenges may be especially problematic in ADRD given that patients may not spontaneously report or recall prior experiences making assessment of blinding success and expected outcomes difficult. In the future, we recommend rigorous sham-control procedures without a crossover design, inclusion of only NIBS-naïve participants, and poststudy assessment of blinding by both Alzheimer's disease participants and their study partners (who may be providing information regarding functional patient outcomes).

Identification of target(s)

With the opportunity to target specific brain regions and networks, NIBS shows potential for symptomatic treatment of Alzheimer's disease-related cognitive decline in global cognition or within specific domains such as memory, language, attention, or motivation. Although brain stimulation sites varied across studies, the rationale for target sites was generally based on neuroanatomical correlates of cognitive dysfunction in Alzheimer's disease. Studies using TMS were able to target cortical regions with greater focality and using MRI guidance, and frequently stimulated brain targets known to be strongly involved in Alzheimer's disease pathogenesis, including the six brain regions adapted from the NeuroAD trial. Knowledge of distributed resting state networks also played a role in the choice of stimulation site, with one study using the precuneus as a TMS target because of connectivity with the default mode network [40▪▪]. Several studies used tES to target symptoms of Alzheimer's disease such as memory, apathy, language dysfunction, or auditory hallucinations. Another tES application used slow oscillatory tDCS during a daytime nap, which aimed to increase the power of sleep-related slow oscillations and sleep spindles to improve memory consolidation [44▪▪]. Although the use of structural and functional neuroimaging can improve the selection of targets for TMS and tES, a major limitation common to all reviewed studies is the lack of appropriate neurophysiological markers to gauge target engagement and monitor response. Modeling of the induced electrical field can help bridge this gap, though the future will undoubtedly require the combination of NIBS with concurrent electroencephalography, MRI, or positron emission tomography imaging. Although a few basic research studies highlight the potential and feasibility of these combined approaches [59–61], they have yet to be applied to clinical trials for ADRD and there remain critical questions about methodology, analysis, and interpretation.

Temporal interference

A commonality across the NIBS techniques included in this review is that their targets are largely restricted to superficial regions of cortex. Exceptions to this rule do exist, namely, that the effects of TMS are polysynaptic and stimulation of deeper regions (such as the cingulate cortex) is possible with certain coils such as the double-cone [62] or H-Coil [63]. However, the physics of electromagnetic induction stipulate that deeper permeation comes at the expense of reduced focality. Similarly, some models of tDCS do suggest that the induced electrical field extends beyond superficial layers, though the effects are always strongest directly adjacent to the electrodes [64]. Given the prominent role of the

hippocampal formation and adjacent structures in Alzheimer's disease pathology (or the basal ganglia in Parkinson's and Huntington's diseases), the ability to directly and selectively target deeper structures has long been a challenging, aspirational goal for researchers and practitioners of NIBS. This may change with a tACS-based approach of temporally interfering electrical fields, or 'temporal interference' [65]. The principles of temporal interference bear some resemblance to those of confocal microscopy, wherein two half-strength photons are directed to collide and thus summate to excite a deeper structure. In temporal interference, two ultra-high frequency oscillations with small difference (e.g., 10 000 Hz and 10 010 Hz) are directed into the brain from opposing areas such that they 'collide' in some deep structure such as the hippocampus. Although the individual frequencies are too high to affect neural tissue, they summate by subtraction, resulting in a stimulating frequency of the difference (e.g., 10 Hz). To date, temporal interference has moved beyond modeling to animal studies, confirming the ability to selectively stimulate deeper structures such as the hippocampus in rodents [65]. In the future, temporal interference may be translated to humans who have or are at risk of developing ADRD [66], which would allow for improved focality of stimulation on deep cortical targets, including medial limbic structures.

Gamma oscillations

Although the studies to date have focused on the use of NIBS to enhance neural activity related to cognition, there is preliminary evidence to suggest that tACS may be able to decrease amyloid deposits in the brain. Working with a mouse model of Alzheimer's disease, Iaccarino *et al.* [67] demonstrated that using optogenetics to entrain fast-spiking parvalbumin-positive interneurons at 40 Hz (i.e., gamma frequency) reduced levels of amyloid-β $(Aβ)_{1-40}$ and $Aβ_{1-42}$ isoforms. In theory, tACS could achieve a similar effect in humans. Indeed, there is an ongoing open-label proof-of-principle study to test the efficacy of daily 1-h sessions of 40 Hz tACS (ClinicalTrials.gov: NCT03290326). Further study is needed to determine whether this approach can lead to a lasting alteration of electrographic cortical rhythms, interact with proteins involved in neurodegeneration, or lead to meaningful clinical improvement in ADRD.

CONCLUSION

NIBS remains an active area of investigation for treatment of ADRD, though the predominance of small, heterogeneous, proof-of-principle studies precludes definitive conclusions. There is currently insufficient evidence to support widespread adoption of NIBS-based clinical treatments for ADRD, but promising results should encourage continued investigation. The future of NIBS as a therapeutic intervention for ADRD will depend on overcoming three major obstacles: the standardization of NIBS stimulation parameters, confirmation of target engagement, and the recruitment of large, well-characterized cohorts with a biomarker-confirmed diagnosis with sufficient longitudinal follow-up. Addressing all of these challenges is a high bar to cross for any individual research laboratory or center, though a failure to do so will keep the field mired in small, heterogeneous, proof-of-principle studies and case reports lacking in scientific rigor. We therefor propose the establishment of a large-scale, possibly international, consortium, with collaboration between academia and industry. Based on the successful model of the Alzheimer's Disease Neuroimaging Initiative [68], methodological parameters should be published in advance and data collected from this consortium should be placed in a repository and made available to independent researchers.

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A.P.L. serves on the scientific advisory boards for Starlab Neuroscience, Neuroelectrics, NeoSync, NovaVision, and Cognito, and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging.

Conflicts of interest

There are no conflicts of interest.

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