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RESEARCH ARTICLE

Therapeutic Noninvasive Brain Stimulation in Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a looming public health crisis that currently lacks an effective treatment. Noninvasive Brain Stimulation (NBS), particularly transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), offers a promising alternative approach to pharmacological interventions for an increasing number of neurological and psychiatric conditions. The aim of this review is summarize data from therapeutic trials of NBS in AD and other dementing illnesses.

Despite the potential of NBS, there is limited theoretical framework and a lack of guidelines for its applications to AD. Several published clinical trials failed to report key parameters of the interventions thus limiting the utility of the study to assess efficacy and safety. Our review concludes with some suggestions for future studies aimed to advance research into NBS as a potential treatment for the symptoms and disabilities caused by AD and to enable comparison of results across trials. Ultimately, appropriately powered, and controlled, multi-site randomized clinical trials will be needed to evaluate the therapeutic potential of NBS in AD.

INTRODUCTION

The Prevalence of Alzheimer's Disease (AD) and Its Costs. [1]; [2]

In 2012, in the United States alone, there were an estimated 5.4 million individuals with AD. This figure includes approximately 200,000 individuals under age 65 with the relatively rare, early-onset form(s) of AD. The remaining 5.2 million individuals with AD were over age 65, making aging the major risk factor for AD. As life expectancy around the world continues to rise, the number of people aged 65 and older with AD is estimated to increase to 6.7 million by 2025. Barring the development of medical breakthroughs to prevent, slow down, or stop the disease, these numbers are projected to continue to increase.

At present, someone in America is diagnosed with AD every 68 seconds. By 2050, one new case of AD is expected to develop every 33 seconds, or nearly a million new cases per year, resulting in an estimated prevalence of 13.8 million, with 7.0 million aged 85 years or older. AD is already the sixth leading cause of death in the United States and the fifth leading cause of death in Americans age 65 years or older. Between 2000 and 2010, the proportion of deaths resulting from heart disease, stroke, and prostate cancer decreased 16%, 23%, and 8%, respectively, whereas the proportion resulting from AD increased 68%. Furthermore, AD is thought to be critically under-diagnosed; thus, the actual numbers of affected individuals may be much larger.

AD imposes a huge financial burden on society that is only expected to get worse. In 2012, more than 15 million family members and other unpaid caregivers provided an estimated 17.5 billion hours of care to people with AD and other dementias, a contribution valued at more than $216 billion. Aggregate payments for health care, long-term care and hospice for people with AD and other dementias are projected to increase from $200 billion in 2012 to $1.1 trillion in 2050 (in 2012 dollars). At present, Medicare and Medicaid cover about 70% of the costs of care and even that amount is likely unsustainable and projected to shrink, hence increasing the financial burden for afflicted individuals and families.

AD thus represents a true threat to society capable of bankrupting our healthcare system, whilst being a huge source of sorrow and suffering for the afflicted and their families. New approaches to address these dangers are urgently needed.

Approaches to Treatment: The Current State of the Field

At present, available treatments for AD have limited efficacy. There are currently five drugs approved by the *U.S. Food and Drug Administration (FDA)* for the treatment of some symptoms of AD. However, at best these medications

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improve symptoms temporarily [3], and their effectiveness varies across patients. Critically, none of the available treatments alters the underlying course of the disease. While research into pharmacological approaches will continue to make progress, increasingly researchers are investigating alternative approaches to slow or halt the disease. These include holistic and lifestyle modification approaches seeking to improve diet, exercise, and social enrichment, as well as targeted therapies such as computerized cognitive training and brain stimulation.

The purpose of this review is to explore the burgeoning research in the use of noninvasive brain stimulation (NBS) as a potential therapy for AD. In the past few years, a number of pilot studies and small clinical trials have highlighted the potential of NBS to improve cognitive functions in healthy individuals [4, 5]. However, there is no consensus about the efficacy of these approaches or their reproducibility [6] We explore the various approaches and methods of NBS that have been tested as therapeutic interventions for AD. Then, we discuss lingering questions of efficacy as well as safety and ethical considerations. Lastly, we shall offer some suggestions as to how future studies might leverage these and other techniques for greater efficacy.

METHODS

A systematic literature search was performed in the following databases: PubMed, MEDLINE and Google Scholar. The following keywords were used: "TMS", "tDCS", "dementia", "Alzheimer's disease", "Noninvasive brain stimulation", "safety", "clinical efficacy". The focus was on original clinical trials designed for therapeutic purposes, and studies that were limited to dementia diagnoses other than AD were excluded. Review papers and the references cited in the identified studies were used to extend the search for further relevant literature.

Of the 50 articles originally identified as suitable, 38 studies were excluded on the basis that they measured NBS effects on healthy subjects or measured cognitive functions following NBS treatments for diseases other than AD, (e.g., Parkinson Disease and depression). The final selection was composed of 12 studies (see Fig. **1** for details about our sample). For each study, the following data were extracted: (i) number of subjects, (ii) patient diagnosis, (iii) study design, (iv) NBS specifics (method, location and protocol used), (v) current medications (if known), (vi) short- and long-term side effects, and (vii) domain of efficacy (main cognitive functions evaluated).

RESULTS

In recent years there has been an enormous influx in articles and research conducted in relation to NBS in general and its application to dementia and AD in particular. A simple search in Google Scholar with the keywords *NBS* and *dementia* results in identification of almost 4,000 articles. However, while numerous reviews emphasize the potential contribution of NBS in the early diagnosis of dementia [7-12], there have been no published clinical trials using TMS as a therapeutic tool for AD since 2012 [13]. Certainly, efforts to identify potential neural biomarkers for early diagnosis of AD are critical [9, 14], but an equivalent effort should be put into the identification of efficacious treatments to minimize the cognitive problems and disabling symptoms, and ultimately to slow down its progression. In this context, the vast majority of the studies reviewed show some positive cognitive effect of NBS on AD patients. However, an analysis of the available literature suggests that currently available methods for brain stimulation offer specific advantages and limitations that should be taken into account where planning an intervention.

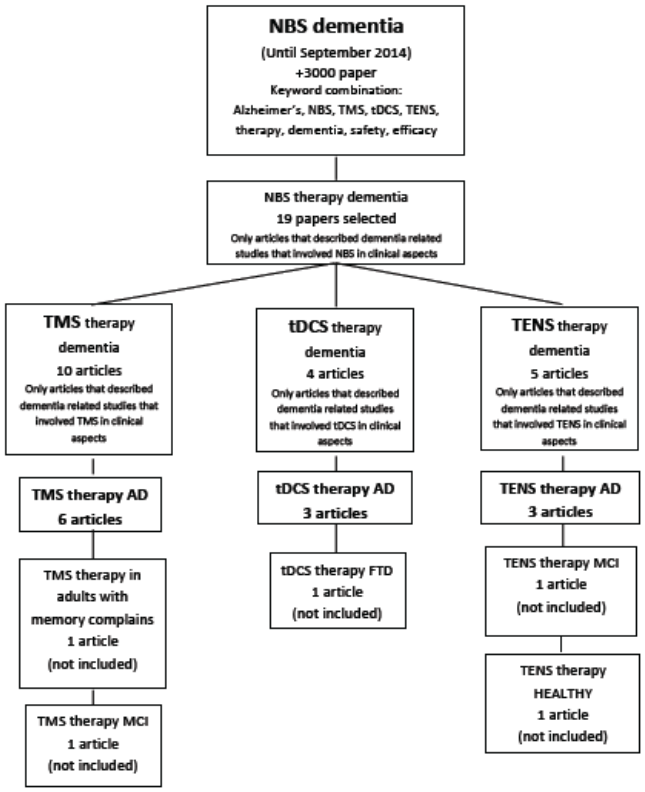

Fig. (1). Diagram selection of the papers included in this review. NBS: Noninvasive Brain Stimulation;TMS: Transcranial Magnetic Stimulation; tDCS: Transcranial Direct Current Stimlation; TENS: Transcutaneous Electrical Nerve Stimulation; AD: Alzheimer's disease; FTD: Frontotemporal Dementia; MCI: Mild Cognitive Impairment.

TRANSCRANIAL MAGNETIC STIMULATION (TMS)

Transcranial Magnetic Stimulation (TMS) was introduced in the 1980's by Barker and colleagues [15]. Since then it has been increasing used to examine brain-behavior relations, to characterize brain physiology in health and disease, and to explore novel therapeutic approaches for various neurological and psychiatric diseases [16].

Mechanism of Action and Procedures

TMS uses Faraday's principle of electromagnetic induction to induce electric currents in specific brain regions: A large brief pulse of electrical current is discharged through a coil (wound copper encased in plastic) and creates a rapidly time-varying magnetic field orthogonal to that coil. Conductive media (including neural elements) affected by the magnetic field can act as pickup coils, in which secondary elec-

tric currents will be induced (depending on their geometry and orientation). The stimulation coil can be shaped in various ways to change the characteristics of the magnetic field, making it more focal (as in the case of a figure-eight design), or reaching greater depths (as in the case of the double cone or the H coils). When the coil is held tangentially against the scalp, the magnetic field penetrates through the skin, skull, and meninges to induce secondary currents in the underlying brain and – if strong enough - leading to neural activation [17]. TMS can be applied targeting various parts of the cortex according to the position of the coil above the scalp. Neuronavigation using frameless stereotaxy devices enables precise guidance and prediction of the directly targeted cortical regions.

TMS pulses can be applied individually (single pulse TMS) to assess cortical reactivity and the integrity of pathways such as the corticospinal tract; in pairs (paired pulse TMS) using different inter-pulse intervals to assess intracortical inhibition and facilitation [18-20]; or as a patterned train (repetitive TMS; rTMS). Applications of rTMS have been shown to induce changes in cortical excitability and modulate activity across distributed neural networks beyond the duration of stimulation itself [21]. While one can raise some theoretical considerations, including modulation of glia activity, reduction of inflammatory responses and longer term modulation of plasticity, at this point there are no experimental data to suggest that TMS alters pathology or is disease course modifying. In most cases, continuous low frequency (1 Hz) stimulation reduces cortical excitability and metabolism, while patterns of high frequency stimulation trains ($\geq$ 5 Hz) typically lead to increased activity in the targeted cortical region. More recently a pattern of rTMS, called Theta Burst Stimulation (TBS; 3 pulses at 50 Hz repeated at 200 ms intervals) has emerged as a means to induce longer lasting changes in brain activity with less stimulation. In most instances, when TBS is applied intermittently (iTBS), cortical excitability can be enhanced, while continuous TBS (cTBS) generally suppresses activity in the directly targeted brain region [22]. The intensity of the pulse governs the effect of the stimulation, as well as contributing to the spread and depth of penetration into the brain. Stimulation intensity is often set for each individual as a percentage of his or her motor threshold (MT), defined as the lowest intensity of stimulation over the motor cortex that elicits a muscle twitch of specific characteristics in at least 50% of delivered pulses.

Safety

TMS has been used in a growing number of laboratories worldwide since 1984. Guidelines for the safe use of rTMS were first published in 1993 by Pascual-Leone *et al.*[23], carefully summarized following a consensus conference by Wasserman in 1998, and were updated in a follow-up consensus conference and recent paper by Rossi *et al.* 2009 [24]. These guidelines have been endorsed by the International Federation for Clinical Neurophysiology (IFCN), been co-sponsored by the US National Institutes of Health, and benefited from input from FDA and other regulatory bodies.

The most worrisome side effect of TMS is induction of a seizure. However, this is a rare occurrence in subjects who do not have epilepsy, or who are not prone to seizures. To date, very few patients or study participants have had seizures associated with TMS reported in the literature, among the many thousands of normal subjects who have received it since 1984 [24]. In a recent review of published studies that applied rTMS to non-motor areas in healthy participants and patients between 1998 and 2003, only two seizures occurred among 3,092 subjects exposed to rTMS [25]. Overall, only 16 seizures have been reported in the world literature and they have occurred in applications utilizing parameters outside current recommendations [24]. The precise risk ratio is uncertain, but the overall risk for this complication is thought to be less than 1/1,000 studies. TMS has also been rarely associated with syncope. Additional side effects associated with TMS, and measures that should be taken to minimize them, are summarized in Table **1.**

Table 1. Risks associated with TMS and measures to prevent them.

Risk Associated with TMS	Measures taken to prevent/ minimize this risk
MILD headaches or neck pain - most common side effect	Solved by acetaminophen (Tylenol®) or other non- steroid steroidal anti inflammatory drugs
Tinnitus or rarely short-term hearing loss caused by some loud clicking TMS	Earplugs offer at each TMS session, demonstrated being effective preventing the risk of hearing disturbance by animal and human studies
Short-term changes in memory, attention and other cognitive functions	Theoretical risk- not found in any current safety study
Acute psychiatric effects (e.g. mania, delusions) in patients with medically refractory depression or bipolar disorder- rare complication	Effects not shown in those without a co-morbid affective disorder
Concentration/memory deficits which are exceedingly scarce.	Brief Mini-Mental State Examination performs before and after every rTMS session

Therapeutic Applications of TMS (Table 3)

In 2008, the FDA approved the Neuronetics TMS device for the treatment of patients with treatment-resistant major depressive disorder (MDD) [26]. Since then, the FDA has also cleared the Brainsway device [27] and most recently the Magstim Super Rapid for treatment of patients with medication-resistant MDD, and the Cerena device [28] for abortive treatment of medication-resistant migraine. Medicare and most major health insurance companies cover the cost of rTMS for patients with MDD, and there are nearly 1,000 clinics offering therapeutic TMS around the world. In addition, several pivotal trials are on the way testing different rTMS devices and approaches for other neurological and psychiatric diseases, and the literature describing trials of NIBS in the treatment of neurologic diseases is growing rapidly (see Fig. **3**). However, most trials using TMS are small, proof-of-principle studies, the placebo response may be substantial, and there are significant challenges to maintain blinding in clinical trials [29].

Table 2. Risks associated with tDCS and measures to prevent them [29].

Risk Associated with tDCS	Measures taken to prevent/ minimize this risk
Tingling, itching and burning sensation	These effects are transient, and disappear within a few minutes after the end of stimulation. Add more saline to the sponges in case the sensation worsens.
Mild headache	Solved within minutes/hours after the session. If needed use acetaminophen (Tylenol®) or other non- steroid steroidal anti inflammatory drugs
Appearance of bright flashes of light (phosphenes) when the stimulation starts and ends the start/end of the stimulation)	This sensation is harmless, just a response of the visual system to a sudden shift in electric voltage.
Others: skin burn, loss of consciousness… Mainly due to involved stimulator malfunction or stimulation parameters outside the normal range.	Perform this techniques in an adequate environment and with the supervision of a proper trainee

To date, there are a number of studies completed in healthy participants that suggest the applicability of TMS techniques in AD. Some studies have shown improvement in verbal memory [30] as well as working memory and executive functioning [5]. In addition, Manenti and colleagues found that rTMS improved episodic memory in young and elderly healthy individuals [31]. Furthemore, a recent meta-analysis by Guse, Falkai and Wobrock [32] highlighted improvements in cognition from high frequency rTMS applied to the dorsolateral prefrontal cortex (DLPFC). Therefore, it is not surprising that translational applications of TMS for therapy in AD have indeed been tried as summarized in the results section below. However, as the results have varied across studies, it should be emphasized that different protocols of rTMS can and will result in different outcomes. Most importantly, it is critical to remember that rTMS is a tool to modulate activity in specific targeted brain regions and their connected networks. Therefore a clear sense of the cognitive function being targeted and its neurobiological substrate is imperative. TMS is likely never going to be a therapy for AD or any other disorder, instead it might offer a valuable approach to reduce disability caused by specific symptoms of a given disease. For a more extensive review, see Fregni and Pascual-Leone [33].

Interventions employing rTMS to enhance cognitive abilities or address cognitive deficits in patients have shown improvements in specific domains depending on the targeted brain region. The picture emerging is consistent with the notion that rTMS can modulate specific brain networks, which in turn represent and support specific cognitive functions. For example, Cotelli and colleagues [34] demonstrated an improvement on auditory sentence comprehension after high frequency rTMS over the left DLPFC. Translational approaches to improve language functions in patients with AD seem possible [35, 36]. Nevertheless, no consistent data has been collected.

Cotelli and colleagues [35] showed an improvement in Action Naming task after applying rTMS over the bilateral DLPFC. Two years later, the same group [36] repeated the study with a bigger sample size (n=24), which allowed them to subdivide participants into groups according to disease severity (i.e., mild AD, moderate-to-severe AD). The authors found a similar improvement in Action Naming task performance in both groups, but only the moderate-to-severe group showed a difference in the Object Naming task. While the results of these studies offer a view into the immediate effects of rTMS, only a single rTMS session was applied and assessments were not repeated following the intervention. Hence, it is not possible to evaluate the duration of the effects of rTMS in AD patients – a critical consideration in assessing potential clinical utility.

Ahmed and colleagues [37] found that patients who received high frequency rTMS showed a significant improvement in the Mini-Mental Status Exam (MMSE) and the Instrumental Daily Living Activity Scale (IADLS), as well as an improvement in mood as measured by the Geriatric Depression Scale (GDS). The authors compared high-frequency and low-frequency rTMS, with the latter showing no significant improvements, and the clinical benefit being present only in the mild/moderate AD group, while the severe AD patients didn't show any significant improvement. These findings indicate that the overall efficacy depends on stimulation as well as patient characteristics, emphasizing the need for parsing analyses according to factors such as disease severity.

In a more recent clinical trial, Rabey and colleagues [13] combined high frequency rTMS of multiple sites with cognitive training for a total of 54 sessions over 18 weeks. A prior study employing the same approach was conducted by the same research team in 2011 [38] as a proof-of-principle pilot study. The results demonstrated a significant and durable (still present at 3 months post-intervention) improvement in the cognitive tests measured in the study (ADAS-Cog and CGDI). The group that received sham rTMS didn't show any improvement. The lack of a control group that received only cognitive therapy makes it difficult to differentiate between the effect of rTMS and the effect of cognitive therapy. A pilot study conducted at the Berenson-Allen Center (PI Pascual-Leone) in a small cohort of 20 patients revealed that real TMS associated with sham cognitive training, or real cognitive training with sham TMS, did not achieve effective cognitive enhancement whilst the combination of real TMS with real cognitive training did. These results are presently under consideration for publication. Therefore, it seems that the effects of rTMS and cognitive training are synergistic. TMS can certainly have mood effects and four different TMS devices are cleared by the FDA for treatment of depression. However, those applications require targeting left dorsolateral prefrontal cortex, rather than other brain regions. Nonetheless, given the possible antidepressant effects of TMS, these were formally assessed ruled out. While other studies only analyzed the immediate effects of rTMS, The study by Rabey *et al.* included a 6 week follow-up evaluation However, given the lack of longer term follow-up one

Table 3. Clinical trials using TMS as a *therapeutic tool* in AD.

ARTICLE	STUDY DESIGN	n	DIAGNOSTIC	SEVERITY AD	MEDICATION	SESSIONS	PARAMETER-LOCATION	METHOD OF ADQUIRING LOCATION	PARAMETER-INTENSITY	EFFICACY DOMAIN	CONCLUSION
Cotelli et al. 2006 [62]	Controlled study	15	AD (NINCDS-ADRDA)	MMSE: 17.8+/- 3.7	All ChEI	1 session of active rTMS	R/L-DLPFC Sham	Neuro-navigation (template MRI) Sham: vertex (Cz 10/20 EEG system)	1 train= 10 pulses- 20 Hz- 600 ms 90% MT	Action-object-picture-naming task (CRL-IPNP) Online assessment	Improvement in Action Naming (both sites) No difference in Object Naming
Cotelli et al. 2008 [63]	Controlled study	24	AD (NINCDS-ADRDA)	12 mild AD: MMSE >=17/30 12 moderate to severe AD: MMSE <17/30	All ChEI	1 session of active rTMS	R/L-DLPFC Sham	Neuro-navigation (template MRI) Sham: vertex (Cz 10/20 EEG system)	1 train= 10 pulses- 20 Hz- 500 ms 90% MT	Action-object-picture-naming task (CRL-IPNP) Online assessment	MILD Group: Improvement Action Naming performance (both sites) No difference in Objects Naming MODERATE- SEVERE Group: Improvement in Action Naming Improvemente in Objects Naming D
Cotelli et al. 2011 [61]	Doble blind Cross over Controlled trial	10	AD (NINCDS-ADRDA)	MMSE 16.2+/-2.7	All ChEI	Group 1: 4 weeks rTMS DLPFC Group 2: 2 weeks DLPFC placebo+2 weeks real rTMS DLPFC 5 sessions a week (total 10 sessions)	L- DLPFC	Neuro-navigation (template MRI)	50 trains= 40pulses-20Hz-2s (28s interstimuli) total 2000 pulses-25 min 100% MT	Cognitive Assesment: -MMSE/ADL/IADL -Picture-naming task -SC-BADA At 4 different time points: a.Baseline b.2 weeks after c.4 weeks after d.12 weeks after	IMPROVEMENT only in auditory sentence comprehension subtest (SC-BADA) Group 2: No significant differences between baseline and 2 weeks of placebo Group 1 and Group 2: Long term significant improvement in SC-BADA 12 weeks time point
Bentwich et al.2011 [65]	Open label study	7	AD (early to moderate) DSM-IV	MMSE: 18-24 CDR score of 1	6 ChEI	-Intensive phase:Daily sessions for 6 weeks (5 days a week) -Maintenance phase: bi-weekly sessions for 3 months	Broca Wernicke R-DLPFC L-DLPFC R-PSAC L-PSAC	Neuro-navigation (subject MRI)	Broca, R/L-DLPFC - 90% MT Wernicke, R/L-PSAC - 110% MT 20 trains of rTMS(2s-10Hz-20pulses each train) 3 brain regions (randomized) each day followed by 1-4 COG task during 20-40s	ADAS-COG /CGIC/ADCS-ADL/MMSE -3 weeks prior -6 weeks after treatment started -4.5 months after treatment tarted	ADAS-COG: Significant improvement after 6w and 4.5m CGIC/ADAS-ADL: improvement with no statistical power (b/c of small sample)
Haffen et al. 2012 [58]	Case study	1	AD (NINCDS-ADRDA)	MMSE 20	ChEI (donezepil) NMDA receptor antagonist (memantine) Venlafaxine	10 sessions (daily sessions workdays) Over 2 weeks	Left DLPFC	5 cm anterior method	10 Hz- 5s (25s interstimulation)-20 minutes 100% MT	Battery of 10 neuropsychologic tests: -4months before the rTMS treatment:T0 -1 month after the last stimulation:T1 -5 month after rTMS treatment:T2	-At T1, cognitive performance improved on 8 of the 10 tests used,especially episodic memory and speed processing. -At T2, cognitive performance worsened in comparison with T1, but improved with T0
Ahmed et al. 2012 [64]	Doble blind Cross over Controlled trial	45	AD (NINCDS-ADRDA +DSM-IV)	MMSE: 6-21 32 mild dementia 13 severe dementia	None (at least 2 weeks before the assessment)	Daily sessions for 5 days	R/L-DLPFC	5 cm anterior method *	Group 1: 20 Hz-5s-20 trains(25s interstimulus) Total 2000 pulses. 90% rMT. interhemispheres Group 2: Continuous rTMS1Hz 2000 pulses 100% rMT (divided into 2 trains -30s interstimulus-33min total)	MMSE/IADL/GDS -Baseline -After last session -1 month follow-up -3 months follow-up	Sham in all three scales: MMSE, IADL, and GDS -Group 2 vs Sham: No difference except for IADL scale -Group 1 vs Group 2: significant difference Group 1 better improvement in all rating scales across the four times of assessment.
Rabey et al. 2012 [59]	Doble blind Cross over Controlled trial	15	AD (DSM-IV)	Mild to Moderate MMSE: 18-24 CDR=1	13/15 were medicated (not specified the type of medication)	5 sessions a week for 6 weeks + 2 session a week for 3 months 54 sessions in total	R/L- DLPFC Broca Area Wenicke R/L-pSCA	Subject MRI guiding Neuronavigation	10 Hz 90% MT: Broca area 110% MT: R/L- DLPFC, Wenicke and R/L-pSCA	ADAS-Cog, CGIC, NPI	Improvement in ADAS-Cog and CGCI at 6 weeks and 3 months time points

Legend: n= number of subjects; NINCDS-ADRDA= National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; MMSE= Mini-Mental State Examination; ChEI= Cholinesterase Inhibitors; DLPFC= dorsolateral prefrontal cortex; pSCA= parietal somatosensory association cortex ; MT= motor threshold; CDR: Clinical Dementia Rating; GDS: Geriatric Depression Scale; ADAS-COG= Alzheimer's Disease Assessment Scale-Cognitive subscale ; CRL-IPNP= Center for research in Language- The International Picture Naming Project ; SC-BADA: Sentence Comprehension subtest- Battery for Analysis of Aphasic Deficits ; IADL: Lawton Instrumental Activities of Daily Living scale ;ADL: Activities of Daily Living Scale; ADCS-ADL: Alzheimer's Disease Cooperative Study- Activities of Daily Living Scale ; NPI: Neuropsychiatric Inventory

*5 cm anterior method= DLPFC stimulation site was defined as being 5 cm rostral in the same sagittal plane as the optimal site for MT production.

can only speculate that the effects are likely limited and will likely require some kind of maintenance protocol.

Such multifocal rTMS combined with cognitive therapy appears to be a promising, safe, noninvasive intervention, capable of providing beneficial effects beyond what is available through pharmacological approaches alone. However, studies to date are small and the controls have serious limitations. Therefore, the true efficacy of an approach based on multiple stimulation sites cannot be ascertained until other research teams replicate the findings and larger, multi-center studies are completed. Similar multi-site approaches to brain stimulation have been shown to be beneficial to patients affected by tinnitus [39], but not in the case of depression [40, 41], suggesting the efficacy of this approach varies by disease and relates to the underlying neurobiology.

Transcranial Direct Current Stimulation

Another major NIBS method is transcranial direct current stimulation (tDCS). The ability of electrical stimulation to evoke a physiological response is not new, having been recognized by Walsh, Galvani, and Volta in the 18th century [42, 43].

Mechanisms of Action and Procedures

In modern applications, tDCS modulates brain excitability via the application of low- amplitude (0.5-2 mA) direct current through electrodes that are attached to the scalp [44, 45]. The current leads to changes in the relative concentrations of anions and cations in the extracellular milieu, which in turn affects the resting membrane potential of neuronal populations in the vicinity of the electrodes. Reports by Nitsche and colleagues demonstrated the capacity of tDCS to modulate motor cortical excitability as evaluated by TMS-elicited MEP amplitudes [46]. Generally, cortical excitability is increased under tDCS anode and decreased under the cathode. Unlike TMS, in which induced currents can be strong enough to depolarize neurons and induce action potentials, tDCS influences spontaneous neuronal activity in a purely neuromodulatory manner [45]. The duration of tDCS after-effects outlasts the stimulation and varies largely as a function of the intensity and duration of the tDCS applica-

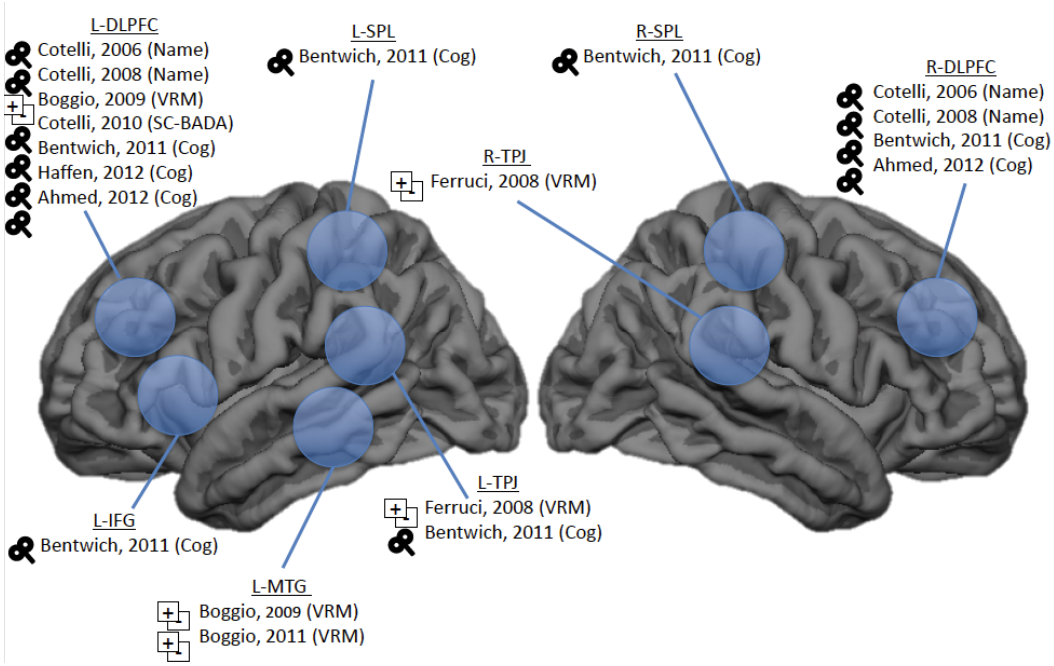

Fig. (2). Illustration of stimulated area in relation to cognitive domain tested.
Locations : right and left dorsolateral eprefrontal cortex (R/L-DLPFC); Broca's area in the left inferior frontal gyrus (L-IFG); right and left temporal parietal junction (R/L-TPJ), including Wernicke's area; left middle temporal gyrus (L-MTG); and snsory association areas in right and left superior parietal lobule (R/L-SPL). *Domains* : action and picture naming (Name); verbal recognition memory (VRM); sentence comprehension (SC-BADA); and general cognition (Cog), including the cognitive subscale of the Alzheimer's disease assessment scale (ADAS-COG), the mini mental status exam (MMSE), and activities of daily living. (ADL)

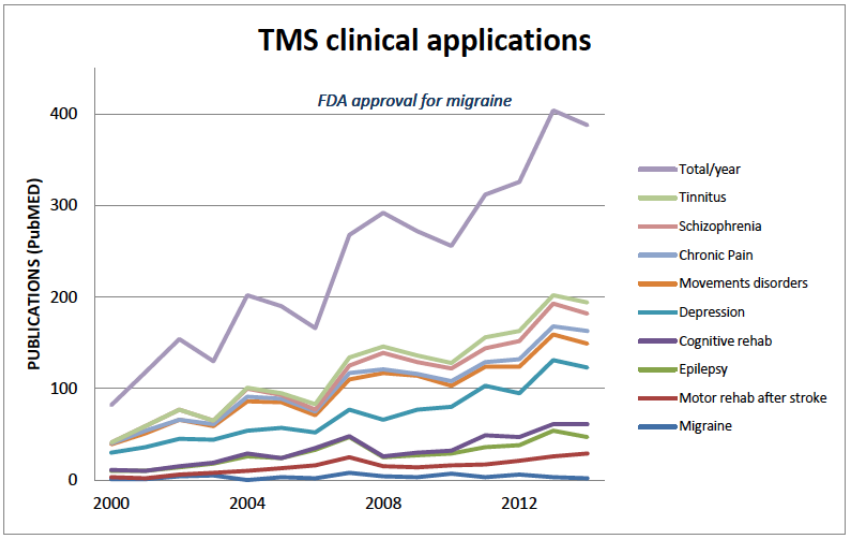

Fig. (3). TMS clinical trials published between 2000 and 2014. Systematic bibliography search in PubMed.

tion [47]. Some reports suggest that repeating tDCS sessions daily for several weeks might further increase the duration of its effects on behavioral outcomes [48]. Short-term effects of tDCS are thought to occur via non-synaptic mechanisms by depolarization of resting membrane potentials [44, 49], whereas longer-term effects are believed to occur through NMDA-dependent mechanisms and appear consistent with use-dependent synaptic plasticity [47, 50]. Further reports have demonstrated the utility of tDCS in the facilitation of several cognitive domains, such as implicit motor learning and visual-motor learning [44, 51].

Safety

The safety profile of tDCS is quite favorable, as many studies have failed to demonstrate lasting adverse effects. Nitsche and Paulus measured neuron specific enolase (NSE), a marker of neuronal injury, following up to 13 min of 1 mA tDCS and demonstrated no change in NSE levels [47]. Commonly reported adverse effects of tDCS include fatigue, mild headache, nausea, and a transient tingling, itching, and/or redness in the region of stimulation [52{Nitsche, 2003 #29, 53]. Poreisz *et al*. concluded after the analysis of 567

tDCS sessions on more than 100 participants that tDCS applied over the motor and non-motor areas according to the present tDCS safety guidelines [44, 53, 54] is associated with relatively minor adverse effects. Table **2** shows the risks associated with tDCS as well as measures to take in order to minimize them. The prevalence and severity of these side effects are related to stimulation parameters determining among others total charge density and charge per phase. However, without an established specific criterion for maximum stimulation dose, the establishment of an objective safety threshold has been difficult to define.

Therapeutic Applications of tDCS (Table 4)

As in the case of TMS, the number of published trials of tDCS in the treatment of neurologic diseases is growing rapidly (see Fig. **4**). However, as for TMS, most trials are small, proof-of-principle studies, and larger, multi-site studies with proper sham-stimulation controls are needed.

Some researchers have demonstrated that tDCS can enhance cognitive function in healthy participants. Relevant findings have included improvements in working memory [55, 56], as well as verbal fluency [53]. The combination of tDCS with other interventions can be achieved with relative ease given the highly portable nature of tDCS device and simplicity of operation. To date, a number of studies have looked at the utility of tDCS-induced neuronal modulation coupled with physical and occupational rehabilitation [57]. Given this evidence, tDCS appears well suited for translational clinical applications in cognitive rehabilitative settings [58]. In addition, tDCS is increasingly used in clinical studies, particularly for neuropsychiatric disorders such as major depressive disorder, chronic and acute pain, stroke rehabilitation, drug addiction, and other neurologic and psychiatric conditions [33, 59]. Recent studies show that tDCS can enhance visual and word-recognition memory in patients with AD [60-62] as well as selective attention, working memory, and word recall [63]. In patients with fronto-temporal dementia, tDCS has been shown to provide similar therapeutic results as in AD patients, including improvements in memory tasks [63], but not verbal fluency [64].

Approaches using tDCS have become very popular in the past years with the launch of several devices. In particular, the ability of these devices to be used for self-administered stimulation has fueled a controversy about cognitive enhancement in healthy individuals (Lapenta 2014, Dubljevic 2014, Santarnecchi *et al* 2013). The effects of tDCS on cognitive functions in healthy humans have been reported in numerous studies (Kuo and Nitsche, 2012). However, as summarized by Kuo *et al.* (Kuo 2014), evidence about the efficacy of tDCS in neuropsychiatric conditions are less consistent.

Table 4. Clinical Trials using tDCS as a *therapeutic tool* in AD.

Article	Study Design	N	Diagnostic	Severity Ad	Medication3	Sessions	Parameter-Location	Method of Adquiring Location	Parameter-Intensity	Efficacy Domain	Conclusion
Ferruci et al. 2008 [41]	Double blind Crossover Controlled trial	10	AD (NINCDS-ADRDA+ DSMIV)	MMSE >20 (22.7+/- 1.8)	ChEI All patients	1 anodal +1cathodal +1sham (random and 1week-interval)	Bileteral TPareas 3rd electrode (cathode) over right deltoid muscle (extracephalic reference)	Manual Measuring -left: P3-T5 -right: P6-T4 according 10-20 EEG international system	1.5 mA 15 minutes	WRT: ADAS-Cog. VAT: Posner Paradigm Time points: Baseline - prestimulation 30min. after stimulation	A single session of: -Anodal tDCS improved WRT accuracy -Cathodal tDCS worsened WRT accuracy -In AT neither protocol induced changes.
Boggio et al. 2009 [40]	Crossover Controlled trial	10	AD (NINCDS-ADRDA)	MMSE 12-25	4 ChEI 16 other neuropychoactive medications	ANODAL tDCS 1- Left DLPFC 2- Left TC 3- Sham (random at least 48h-interval)	Left DLPFC Left TC	Manual Measuring -left DLPC: F3 -left TC: T7 according 10-20 EEG international system	2 mA 30 minutes	-VRM - SA:Stroop - WM: Digit Span *Testing after 10 min. until the end of stimulation	After a single session of tDCS -Enhancement on a VRM task after tDCS of DLPFC and LTC - No significant effects in WM or SA.
Boggio et al. 2012 [69]	Double blind Cross over Controlled trial	15	AD (NINCDS-ADRDA+ DSMIV)	MMSE >15	8 ChEI	ANODAL tDCS and sham (7.1+/- 5.8 days-interval) 1 session 5 consecutive days	Bilateral Temporal Cortex 3rd electrode over right deltoid muscle (extracephalic reference)	Manual Measuring -scalp electrodes: T3- T4 -left TC: T7 according 10-20 EEG international system	2 mA 30 minutes	Cognitive Assessment: MMSE/ADAS-Cog/VRM-IBV/VAT: Posner task. Time points: -Before the first tDCS session -At the end of treatment day 5 -1 week later -1 month later	VRM improved after 5 tDCS daily sessions and persisted for 4 weeks after stimulation. No significant changes in ADAS- Cog, MMSE or VAT.

Legend: n= number of subjects; NINCDS-ADRDA= National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; MMSE= Mini-Mental State Examination; ChEI= Cholinesterase Inhibitors; DLPFC= dorsolateral prefrontal cortex; TP= Temporoparietal ; TC= Temporal Cortex ; ADAS-COG= Alzheimer's Disease Assessment Scale-Cognitive subscale ; WRT= Word Recognition task; VRM= Visual Recognition Memory task; SA= Selective Atention; WM= Working memory; IBV= software for the development of computerized assessment tasks; VAT= Visual Atention Task.

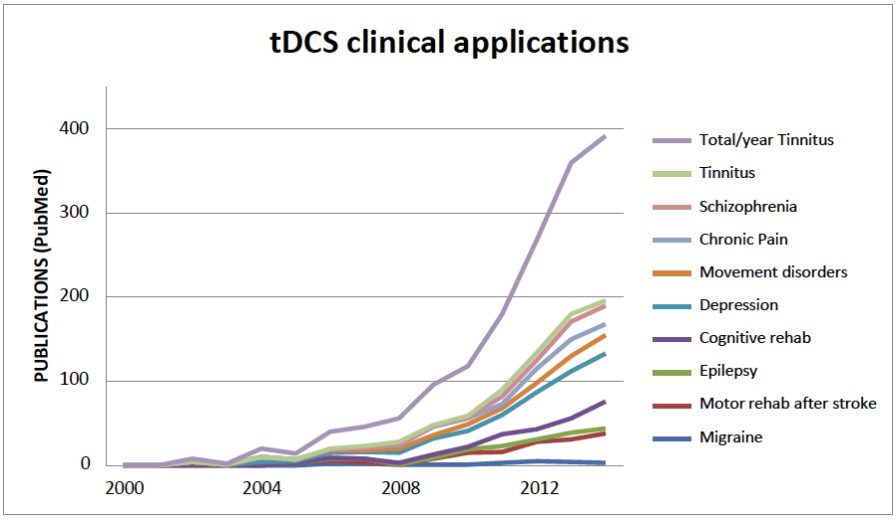

Fig. (4). tDCS clinical trials published between 2000 and 2014. Systematic bibliography search in PubMed.

Only three papers met the inclusion criteria for the present review of tDCS as a therapeutic intervention in AD. These are small, limited studies, but they show positive and consistent results. Ferruci and colleagues [61] reported an improvement in the performance of the Word Recognition Task (WRT) after a single session of tDCS with anodes over bilateral temporo-parietal areas (compared to sham tDCS). By comparison, tDCS with cathodes over the same bilateral temporo-parietal regions led to a worsened performance when compared to sham. These effects were task-specific and no significant changes in the performance of the Visual Attention Task (VAT) were reported. In another study, Boggio *et al* [60] reported an enhancement on Visual Recognition Memory (VRM) task following a single session of tDCS with the anode over the left DLPFC or left temporal cortex Again, these effect were limited to a single task and no significant effects were shown for working memory (WM) or selective attention (SA). Given the promising results, the same group designed another intervention study to investigate the long-lasting effects of tDCS [65]. By applying tDCS for 5 days with anodes over bilateral temporal cortices, AD patients improved their performance at the VRM task, with the effect being persistent after 4 weeks from the last stimulation session. As reported by Ferruci, no significant changes in the score at the Visual Attention task (VAT) or any other cognitive assessments were observed.

Transcutaneous Electrical Nerve Stimulation (Table 5)

The ability of electricity to relieve pain has been known for thousands of years, with the first written document by Aristotle [66]. Transcutaneous Electrical Nerve Stimulation (TENS) has been used since the 1970's mainly for relieving pain [67].

Mechanisms of Action and Procedures

TENS involves applying electrical stimulation over the skin, which activates underlying nerve terminals. While TENS is not direct brain stimulation *per* se, it could affect brain and cognitive functions through the afferent modulation of the somatosensory system. TENS applied to peripheral nerve fibers can activate central nervous system structures such as the hippocampus and hypothalamus, thus affecting memory processes, affective behavior and circadian rhythms [68]. Clinically, TENS is applied at varying frequencies, intensities and pulse durations. Frequencies are classified as high frequency (≥ 50 Hz), low frequency (≤ 10 Hz) or burst (bursts of high frequencies applied at a lower frequency). Intensity is determined according to the patient's own feeling and level of sensation. Generally, intensity is raised until the patient reports a noticeable but comfortable tingling sensation [69, 70]. Different TENS techniques are used to selectively activate different populations of nerve fibers. Specific applications arise from combining different levels of intensity (low, high) and frequency (low, high) [69].

Therapeutic Applications

A series of articles by Scherder and colleagues have reported that TENS can be used to enhance cognitive functions in patients with AD and mild cognitive impairment (MCI) [71, 72]. The results are intriguing, but replication by other research teams seems critically needed.

Even though the literature about TENS in AD has not significantly grown in the last 15 years, it was included in the present review given the promising results shown by the studies by Scherder and colleagues. In their first study in 1995 [67] the authors showed how the application of TENS for 30 min a day for 6 weeks had a positive effect on verbal long-term memory, as well as on short and long-term visual memory. In addition, they also documented an improvement in other the cognitive domains lasting as long as 6 weeks after the last training session. In a follow-up study applying the same protocol [72] positive effects in additional cognitive domains were also documented. Specifically, the authors found a positive effect on short-term visual memory, face and picture recognition, verbal fluency, as well as a beneficial influence on patients' independence participation in daily life activities. These effects were limited to cognitive abilities and no significant improvements were seen in measures of affective behavior.

Table 5. Clinical trials using TENS as a *therapeutic tool* in AD.

Article	Study Design	N	Diagnostic	Severity Ad	Medication	Sessions	Parameter-Location	Method of Adquiring Location	Parameter-Intensity	Efficacy Domain	Conclusion
Scherder et al. 1995	Controlled trial	16	AD: NINCDS-ADRDA	CST=10.6 (average) Early stage AD	Not mentioned	Daily sessions for 6 weeks; 30 min a day	Patient's back Between Th1 and Th5 2cm from diameter - different side every day	Observation	BURST-TENS: 9 trains, 160Hz, 2 Hz repetition, pulse duration of 40μs	Neuropsychological tests. Evaluation of: MEMORY Digit span (WMS-R) Visual Memory Span (WMS-R) The 8 Words Test Face Recognition (RBMT) Picture Recognition (RBMT) Word Fluency	Positive effect on verbal long-term memory and on visual short-term and long-term memory. The improvement in some domains remained after 6 weeks without treatment.
Scherder et. al 1998	Controlled trial	18	AD: NINCDS-ADRDA	CST=10.4 (average) Early stage AD	Not mentioned	Daily sessions for 6 weeks; 30 min a day	Patient's back Between Th1 and Th5 2cm from diameter - different side every day	Observation	BURST-TENS: 9 trains, 160Hz, 2 Hz repetition, pulse duration of 100μs	Neuropsychological tests. Evaluation of: MEMORY Digit span (WMS-R) Visual Memory Span (WMS-R) The 8 Words Test Face Recognition (RBMT) Picture Recognition (RBMT) Word Fluency +2Observational Scales: BOP +Behavior Inventory	Positive effect on short-term visual memory, Face and Picture recognition, Verbal fluency, as well as beneficial influence on patients' independent participation in daily life activities. Some of the effects can be seen up to 6 weeks after the treatment. No positive effect on Affective Behavior.
Scherder et al. 1999	Controlled trial	16	AD: NINCDS-ADRDA	MMSE<=17 GDS: 6 stage Mild Stage AD	Not mentioned	Daily sessions for 6 weeks; 30 min a day	Patient's back Between Th1 and Th5 2cm from diameter - different side every day	Observation	BURST-TENS: 9 trains,160Hz, 2 Hz repetition, pulse duration of 100μs	Neuropsychological tests. Evaluation of: MEMORY Digit span (WMS-R) Visual Memory Span (WMS-R) The 8 Words Test Face Recognition (RBMT) Picture Recognition (RBMT) Word Fluency +2Observational Scales: BOP +Behavior Inventory	TENS has a positive effect on performance of mid stage AD patients on Visual Memory Span, but no therapeutic effect on the patients' physical, social or effective functioning. .

Legend: n= number of subjects;NINCDS-ADRDA= National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; MMSE= Mini-Mental State Examination; GDS= Global Deterioration scale; CST= Dutch Cognitive Screening Test ; RBMT= Face Recognition from the Rivermead Behavioural Memory Test ; WMS-R= Digit Span from the Wechsler Memory Scale–Revised; BOP=standard factor-analyzed rating scale for elderly patients

In a third study by the same group [68] the impact of TENS was assessed in AD patients at more advanced stages. A positive effect on Visual Memory Span was observed, with no effects on other cognitive and functional tests (e.g.: Beoordelingsschaal voor Oudere Patienten: BOP- a revision of the Stockton Geriatric Rating Scale), where few subscales where tested, being the main one "Need of Help", which concerns subject's independence of activities of daily life; and the Behavior Inventory, meant as an affective supplement to the BOP, evaluating depression, elation, shyness, mood, anger, tiredness, activity, anxiety, conscience, indifference, cognition, and contact of the participants).

These results suggest that TENS might be more effective in earlier stages of AD than in more advanced stages. Overall, while such positive results are encouraging, it is worth emphasizing that the mechanisms of action of TENS for cognitive enhancement and restoration is completely speculative and unclear, and there is a need to replicate the findings are a different laboratory and with appropriate control conditions before embarking in larger trials.

DISCUSSION

In summary, approaches using tDCS and rTMS can produce selective improvements (e.g., improved object naming) when applied to a given, appropriate brain cortical target (e.g., DLPFC) to modulate activity in a specific neural network engaged in the cognitive function targeted. When the intervention is repeated daily additive effects can be induced

and the behavioral/cognitive impact can last longer and has the potential to become clinically significant. In AD, given the deterioration of multiple cognitive functions supported by multiple, different neural networks, targeting several cortical regions while engaging in cognitive training of their various supported cognitive functions appears to be most promising. With such approaches, a more generalizable, clinically meaningful and long-lasting improvement (e.g., improving ADAS-Cog scores for up to 4.5 months) has been observed, and warrants follow-up. TENS might lead to improvement in memory and picture naming as well as a modest improvement in ADLs and affective behavior, although findings may have been confounded by study design and replication is needed. Overall these results are encouraging, but there have been too few studies conducted to date, sample sizes are too small, control conditions need more attention, and it is premature to be overly optimistic.

Limitations of Studies to Date

General limitations of the studies to date fall into two broad categories: (1) how the intervention was designed, and (2) how the outcome was assessed. The primary limitation of most of the studies is that they were completed using relatively small sample sizes (average = 19.5 patients), underscoring the need for appropriately powered studies to better understand the impact of NBS. Secondly, most of the studies were not double-blind controlled trials. In clinical studies, the confounding effects of expectation on the part of the patient, but also the researcher, are well known and represent a serious issue [73]. In a 1995 study [71], significant positive effects of TENS on affective behavior were observed when the treatment was administered to patients while the therapist was present in the room. By contrast, the same intervention was subsequently found to be ineffective when the therapist was not observing the treatment [72]. This example illustrates how crucial it is to report on and control for every possible aspect of a therapeutic intervention. For instance it is important to consider whether: (i) was the patient alone during the treatment? (ii) Was there a therapist or family member in the room with them? (iii) to what extent did the clinician/researcher interact with the patient before, during, and after the treatment? All of these factors have to be taken into consideration and should be carefully defined a priori to create consistent protocol. This is especially important when dealing with certain group of patients, like those suffering from various forms of dementia, who may bring different levels of intrinsic motivation and compliance to the study protocol.

The second important general limitation of the studies reported to date is the lack of consistent methods of assessment. While some studies used standard measures for evaluating patients' outcome, such as the Cognitive subscale of the Alzheimer's disease Assessment Scale (ADAS-Cog), and the Mini Mental Status Exam (MMSE), others used only rather specific tests such as the Sentence Comprehension subtest of the Battery for Analysis of Aphasic Deficits (SC-BADA) and the Verbal Recognition Memory task (VRM). While it is important to capture a wide range of potential outcomes, especially during the early phase of assessment of a novel intervention, the use of specialized cognitive tests makes it difficult to make effective comparisons across studies and evaluate true clinical significance. In addition, most studies differ in the times at which the outcomes were assessed. Some focused on improvements at short and medium-range time points: immediately after treatment and up to a 6-week follow-up [74]. However, other studies only assessed the outcome immediately after the intervention (e.g. [13]), while others (e.g. [75]) only reported findings 1 month after treatment. In order to explore clinical meaningfulness, it is imperative that future studies test cognitive functions at multiple time points, including later times, such as 3-6 months post-treatment, to assess whether or not the treatment can induce long-term benefits.

Defining the Cortical Target

AD is a progressive neurodegenerative disease, in which numerous cognitive impairments result from the progressive degeneration across multiple brain areas and brain networks. As a result, AD patients can differ broadly in terms of their profile of cognitive deficits as well as symptom severity. Nevertheless, most studies have applied NBS primarily to the DLPFC, while only a few stimulated other areas as well [74]. As a result, the most widely reported outcome was an improvement in working memory (which is strongly linked to DLPFC function), with only a few improvements documented in other cognitive domains. Even if real, an improvement in working memory is hardly a clinically meaningful therapeutic effect for the broad cognitive impairment of patients with AD. A better approach would be to assess each patient and specifically target different brain regions, according to each patients' specific cognitive impairments, or consider targeting multiple brain regions and networks linked to the core cognitive deficits of patients with AD within the same session [13]. Following the successful model for the treatment of movement disorders [75-77], stimulation could be targeted to accessible brain regions based on their effective functional connectivity with deeper structures out of reach by noninvasive techiniques.

As shown in the Fig. (**2**), there is no consensus regarding which brain region(s) should be targeted in AD. Most of the studies (6 out of 12 analyzed), chose the DLFPC given evidence of its role in action naming [78], object naming [79], and spatial memory [80]. However, even within these studies, half stimulated only one hemisphere and the other half stimulated bilaterally. Part of the problem is that many of these studies do not appear to be strictly hypothesis-driven. That is, they don't start from a model of how the progressive deterioration in AD leads to a breakdown in brain networks that support various cognitive functions, and then seek to restore function by targeting the affected networks or nodes within a network. Instead, these studies target a task or set of tasks that have been shown to be impaired in AD (e.g., picture naming), identify a brain region (e.g., DLPFC) whose function is believed to be critical for the particular task, and stimulate that region. While this approach may help establish a brain-behavior relationship in AD, it will likely not do much to change the disease's trajectory.

Targeting of Specific Brain Regions – Neuronavigation

Given the large variability in the response to TMS effects in both clinical and general populations [81, 82] it is crucial

to precisely define and appropriately localize the targeted region. This is even more crucial when stimulation is repeated over multiple days, when a consistent target must be achieved across sessions. In this regard, recent advances in TMS neuronavigation techniques [83-85] allow the use of subject-specific MRI data to accurately guide and maintain placement of the TMS coil on the target. In addition, functional MRI (fMRI) or positron emission tomography (PET) data can be also used as a functional navigation map, such that the target can be selected on the basis of its association with specific cognitive functions or its connectivity with other regions of interest. To date, many researchers have chosen scalp locations based on anatomical landmarks (such as the "10-20" system for EEG electrode placement) or using an arbitrary distance from the motor cortical representation of the dominant hand, obtained by eliciting a motor evoked potential (MEP) correspondent to the FDI muscle twitch.

While MR-guided methods undoubtedly increase the consistency of the stimulation location within and across trials, there is not enough data to determine whether traditional or neuronavigated approaches might yield greater efficacy in the case of AD. Answers to these questions should be the focus of future studies.

Domains of Efficacy

Most studies reported in this review used specific scales to measure improvements in specific domains. One example is the use of various cognitive tests in order to assess the improvement of different aspects of working memory (e.g. Verbal Recognition Memory task, VRM). Fig. (**2**) shows the variety of domains tested in the studies included in the present review. Aside from the inability to compare the results from the different studies, there is also a question whether some of these actually translate to real benefits in the everyday life of AD patients. It is crucial to conduct large scale studies that will not only assess specific cognitive functions using standardized tests, but will also gather reports from caregivers and family members of patients to evaluate the impact of the intervention on activities of daily living in more ecological settings. It is imperative to aim for beneficial effects in real life and daily performance. Some studies reviewed [34, 37, 38, Ahmed, 2012 #59, 45, 74, 75, 86] did use more comprehensive cognitive tests such as MMSE or ADAS-Cog to measure the cognitive improvements. While the ADAS-Cog is broadly accepted as meaningful, the MMSE is probably not sensitive enough. Future studies have to focus on comprehensive and standardized methods of assessment to enable clinically relevant conclusions.

Recommendations for Future Trials of NBS in AD

Based on a careful analysis of the limitations that the NBS research studies published to date, we offer a few suggestions for future studies to tailor interventions in a more clinically directed approach.

1) Guide Intervention on the Basis of Individual Cognitive Profile

As mentioned in the previous section, most studies have focused on improving specific cognitive domains, regardless of the patients' specific cognitive impairments. However, as demonstrated by Bentwich and colleagues [38], individualized treatment can be achieved in a relatively simplistic manner by matching the location of stimulation to the cognitive domain under investigation. Fig. (**2**) illustrates the relationship between the locations of stimulation and the cognitive domains that were affected as a result. Even though some of this variability in effect could be attributed to differences in the sample size of studies, it is evident how different effects and improvements can be due to stimulation protocol affecting specific domains. Therefore, future studies and therapy interventions should take into consideration the specific impairments of each patient, and consider individualizing a suitable treatment accordingly.

2) Guide the Intervention on the Basis of Disease Severity

Some studies have suggested the potential of TMS to differentiate different stages of progression of AD [87, 88] based on measurements such cortical excitability, the efficacy of intracortical inhibitory circuits, and the magnitude and duration of induced plasticity from rTMS. The use of TMS as diagnostic tool in AD [21, 88, 89], to classify different stages of AD [87] and distinguish between different types of dementia (e.g. AD vs. FTLD) [90, 91] has been the subject of previous reviews and appears worth considering in the future. Showing that a given neural substrate (e.g. connectivity in a given neural network or efficacy of mechanisms of plasticity) is modified by the NBS intervention and accounts for a significant portion of the cognitive effects, would lend greater credibility to the therapeutic potential of the NBS in AD.

Moreover, several studies suggest that disease severity impacts the efficacy of NBS. For example, Cotelli and colleagues [34] demonstrated that applying the same procedure on patients in different phases of dementia and AD leads to different results. Even though the observed differences between cohorts might be the result of other unmeasured variables, these studies suggest that there is a benefit from segregating participants based on disease severity, and caution that the efficacy of a particular treatment may vary dramatically depending on the stage of AD.

3) Guide the Intervention on the Basis of Genetic Profile

Large strides have been made in investigating the pathophysiology of AD [92, 93]. The leading hypothesis about the cause of AD argues that amyloid-β (Aβ) plays an important role in a cascade of events ending in synaptic dysfunction and cell death, "plaques" and "tangles" depositions, and neural network breakdown [94, 95]. Apolipoprotein E (ApoE) binds to Aβ, influencing both Aβ aggregation and the clearance of soluble Aβ [96, 97]. Individuals who carry the ApoE ε4 allele, show increased risk of AD (e.g., [98] in a dose-dependent manner [99, 100]. Wolk and Dickerson [101] have shown that the presence of APOE-ε4 differentially influences large-scale brain networks and this contributes to the clinical phenotype of AD. Pena-Gomez and colleagues [102] found that genetic variations in the gene APOE had effects on the network connectivity changes induced by rTMS.

A number of other genetic factors have been identified that relate to regulation of human brain plasticity [103]. For example, the gene that regulates brain derived neurotrophic

factor (BDNF) plays an important role in neuroplasticity [21]. The BDNF Val66Met polymorphism has been shown to differentially modulate human cortical plasticity and the response to training [104], brain stimulation [105] and motor learning [106]. Recently, the low-activity Met66 allele was shown to be an additional risk factor for rapid disease progression during the preclinical period of AD [107] and may also constitute a risk factor for the development of psychotic symptoms in AD [108]. Genetic predispositions, such as an individual's BDNF or ApoE status, will likely affect both their predisposition to developing AD as well as their receptivity to neuromodulation. Therefore, genetic variations will likely need to be taken into consideration when assessing the efficacy of a NBS intervention. Ultimately, they may lead to tailoring interventions by genetic profile, but for now, this information can be used to parse the analysis based on genotypic variation within the population.

4) Guide the Intervention on the Basis of Neuroimaging Markers

AD is a progressive disease that affects multiple cognitive domains. For that reason, the potential efficacy of multifocal NBS therapy should be taken into account. There are two fundamental approaches: (1) targeting multiple networks individually, with each network/region linked to the primary affected behaviors or/and functions of an individual; (2) Alternatively, it may be possible to identify a single core network, whose dysfunction results in a breakdown of other systems downstream leading to a variety of symptoms, and target that specific site for stimulation. A good example of the latter approach is in Parkinson's Disease, where the degeneration of the dopaminergic neurons in the *substantia nigra pars compacta* (SNc) leads to a breakdown in the direct and indirect pathways of the basal ganglia [109].

At present, there is research that supports these two different approaches. Deep Brain Stimulation (DBS) techniques aim for the approach of modulating the networks underlying the pathophysiology of a disease. The success of DBS is predicated on the ability to identify the core networks responsible for a specific disease in advance. Another example is Obsessive Compulsive disorder, where the brain network responsible for the symptoms is known (dysfunction of the nucleus accumbens, NAc, and its connectivity with the frontal cortex; DBS targeted NAc). In these cases, DBS could be effectively targeted to the abnormal circuit at the core of the dysfunction, rather than targeting those regions downstream that were subsequently affected [110]. There is reason to believe this approach might work for AD as well. Given evidence that AD patients show abnormal resting-state functional connectivity within the Default Mode Network [111], it may be possible to identify and target a core node which underlies this dysfunction. Supporting this line of research, Laxton *et al*. [112] have shown positive results when administering DBS to fornix and hippocampus in AD patients. While behavioral changes were not assessed, the stimulation nonetheless drove physiologic activity and produced large and sustained changes in glucose metabolism in brain regions that were thought to be dysfunctional.

TMS and tDCS studies to date have aimed for the target of multiple networks individually. As is observed throughout this review, the target areas for NBS were single brain regions or multiple sites one after another. A number of recent studies have attempted to mimic the effects of deep brain stimulation technique [113-115]through the use of a TMS "multi-coil" that is capable of stimulating multiple brain areas at the same time. Similarly, there is an active effort to develop the right montage and protocol for multifocal tDCS based on fMRI functional connectivity patterns [116]. Certainly, it is a primary aim of the current research on NBS in AD to integrate, with neuroimaging data to determine the best setup for stimulation.

CONCLUSION

Methods of NBS are increasingly being explored as novel therapeutic approaches to AD. Whilst results are promising, there is a lack of well-tested, hypothesis-driven, appropriately powered and controlled trials. This review examined the 12 studies that tested the potential of TMS, tDCS or TENS as a therapeutic intervention for AD. Due to the relative paucity of studies and no established treatment guidelines, a detailed comparison of approaches or meta-analysis would be premature. Given the wide range of approaches, the results are fairly specific to factors such as brain region targeted and the cognitive domain tested. However, these proof-principle trials reveal stimulation-associated improvements in memory and certain cognitive tests. Approaches that targeted multiple brain regions over daily sessions seemed to produce the most robust positive effects. Thus, despite the relative immaturity of the field, NBS techniques and specifically rTMS, represent a compelling area for research with high potential for therapeutic implications in patients with AD.

FINANCIAL DISCLOSURES

A.P.-L. serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Axilum Robotics, Magstim Inc., and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) and magnetic resonance imaging (MRI). The authors declare no competing interests.

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CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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