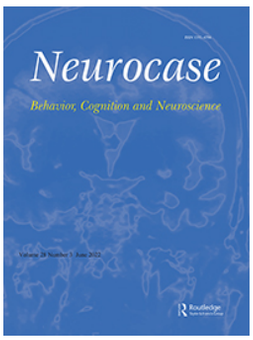

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A four-month home-based tDCS study on patients with Alzheimer's disease

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ABSTRACT

In the present open-label study, our first aim was to study the tolerability and feasibility of long-term treatment with transcranial direct current stimulation (tDCS) and the second aim was to measure whether the treatment led to cognitive improvement. Participants with AD used a tDCS home-treatment kit inducing a low current (2 mA) via two scalp electrodes 30 minutes daily for 4 months. A total of 8 participants were recruited. The treatment technique was manageable for the participants and their spouses, and no troublesome side effects were reported. No significant effects of treatment were found after 4 months.

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Alzheimer`s disease; transcranial direct current stimulation; tDCS; neuromodulation; treatment

Introduction

Alzheimer's disease is neurodegenerative, with atrophy commencing in the hippocampus, entorhinal cortex, and surrounding areas in the medial temporal cortex (Frisoni et al., 2010; Mosconi et al., 2007). Functional magnetic resonance imaging studies have shown decreased activation in these areas during memory tasks in patients with Alzheimer's disease (Remy et al., 2005). Moreover, the disease is associated with impaired neuroplasticity (Koch et al., 2012; Kumar et al., 2017).

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that may enhance neuroplasticity, which is disrupted in Alzheimer's disease (Rajji, 2019). By applying low current (1–2 mA) via two or more scalp electrodes, tDCS modulates cortical excitability by altering the resting membrane potential of neurons, depending on the current flow direction (Nitsche, Fricke et al., 2003). Anodal stimulation modulates the resting membrane potential toward depolarization, increasing the chance of spontaneous firing and the excitability of multiple neurons under the stimulation site (Medeiros et al., 2012). Moreover, anodal tDCS show synaptic after effects, with mechanisms consistent with use- dependent synaptic plasticity (long- term potentiation; Hansen, 2012; Nitsche, Fricke et al., 2003; Stagg & Nitsche, 2011). The involvement of NMDA receptors in tDCS- after effects are proven in pharmacological studies with NMDA inhibitors suppressing the effect of anodal tDCS (Liebetanz et al., 2002). Anodal tDCS also cause a decrease in GABA and increase in glutamate (Stagg et al., 2009). Both GABA and glutamate, being respectively inhibitory and excitatory neurotransmitters, are crucial mediators of LTP.

tDCS has been tested in both healthy participants and patients suffering from psychiatric and neurological conditions in hundreds of clinical trials. The method is considered both safe and well tolerated (Bikson et al., 2016; Nitsche, Liebetanz et al., 2003).

Meta-analyses on tDCS studies in Alzheimer's patients show relatively optimistic results. However, the data are inconsistent, and existing RCTs are limited by small sample sizes (Cai et al., 2019; Hsu et al., 2015; Rajji, 2019). Cai et al reported that tDCS significantly improved cognitive functions in patients with AD (standardized mean difference: 0.37; Cai et al., 2019). Whether tDCS treatment is superior/inferior to other interventions is not clear. Alternative method designs, such as increasing the number of treatment sessions and assessing the long-term effects, can be useful when studying tDCS in Alzheimer's patients.

Multiple tDCS sessions to Alzheimer's patients have shown to improve cognitive function (Im et al., 2019; Khedr et al., 2014) and memory performance (Bystad et al., 2017). However, several separate visits to a research lab can be a burden for both patients and caregivers. Thus, patients with Alzheimer's disease can be difficult to recruit to clinical trials (Clement et al., 2019; Grill & Karlawish, 2010). Trials designed with a large number of visits will likely increase drop-out rates and reduce the probability of achieving sufficient sample sizes. A study by Valiengo et al., 2013 reported that participants listed the burden of regular visits as the main reason why they dropped out of multiple session-tDCS clinical trials (Valiengo et al., 2013). New approaches with less frequent visits to a research lab are needed to ensure that potential participants with Alzheimer's disease can participate in tDCS clinical trials. A solution may be to shift tDCS from clinics to home-based applications.

tDCS equipment is inexpensive compared to other non-invasive brain stimulation techniques. The apparatus is also portable, which makes treatment from home possible. Although the majority of tDCS studies on Alzheimer's patients have been carried out in clinical settings, two have had home-based designs. These two studies, an RCT study by Im and a case study by Bystad, have shown promising results after months-long treatment with daily tDCS sessions (Bystad

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et al., 2017; Im et al., 2019) . The results by Im and colleagues showed that anodal stimulation over the left dorsolateral prefrontal cortex improved participants' scores on the MMSE and the Boston Naming task compared to the sham group. They also registered stabilization in glucose levels in the group receiving stimulation, while a decrease was reported for the sham group. The active group received daily sessions of stimulation for 30 minutes over 6 months. The case study by Bystad et al. (2017) was the longest reported tDCS study for patients with Alzheimer's disease. In that study, a man diagnosed with Alzheimer's disease received daily 30-minute sessions of tDCS, with anodal stimulation over the temporal lobe, over 8 months. The results showed a 39% improvement in immediate recall performance and a 23% improvement in delayed recall performance, in addition to the preservation of general cognitive function as measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

Clinical guidelines for remotely supervised tDCS suggest that to keep home-based tDCS safe and well tolerated, follow-up visits from researchers are important to ensure correct use of the tDCS device (Charvet et al., 2015). Other important factors to reduce dropout rates are hands-on training and prefixed electrodes, both of which safeguard correct placement and make the devices easier to use (Hagenacker et al., 2014).

Aims of the study

In the present study, home-based, self-administered tDCS was offered to eight patients with Alzheimer's disease. The patients, with help from their caregivers, received 30 minutes of 2 mA anodal stimulation daily over the left temporal lobe, aiming to reach the hippocampus, entorhinal cortex and surrounding areas that are essential for memory performance. These areas are affected early on in Alzheimer's disease (Dickerson & Sperling, 2008). As in the majority of previous Alzheimer's studies with anodal tDCS stimulation over the left medial temporal lobe, the return electrode was placed over the right frontal region(Cai et al., 2019). The protocol was also similar to the one used in our previous case study with promising results (Bystad et al., 2017). Our first aim was to study both the tolerability and feasibility of long-term, home-based tDCS in Alzheimer's patients, and our second aim was to measure potential changes in cognition. To measure whether tDCS influenced cognitive functions, cognitive tests were administered before the first tDCS session and after four months of daily stimulation. The patients were also retested four months after the tDCS sessions ended.

Methods

Participants

Participants aged 60–75 years who had participated in a previous tDCS study (with an accelerated design that lasted one week (Rasmussen et al., 2021)) were recruited for the present home-based study. Patients had to meet the diagnostic criteria of probable Alzheimer's disease according to the revised National Institute of Neurological and Communicative Disorders and Stroke Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 2011). We followed Section 4.2: "Probable Alzheimer's disease with increased level of certainty." These criteria included evidence of a progressive cognitive decline based on cognitive and/or neuropsychological evaluation and information from informants (relatives). We set a four-month period from the last tDCS study to enrollment in the current study. If participants were medicated for AD (e.g., cholinesterase inhibitors, memantine), our inclusion criterion was that participants maintained a stable dose over the last three months, and the participants were encouraged to not discontinue the medication during the follow-up period. Participants were also required to live with a caregiver since the study was home-based. The exclusion criteria were metallic implants in the head or a history of seizures, severe illness, psychosis or depression (measured with a Cornell Depression Scale score over 11 (Alexopoulos et al., 1988)). Participants' Mini Mental State Examination (MMSE) scores had to be 17 or higher.

Study protocol

This study was an open label trial in which equivalent treatment was given to all participants over a 4-month period, followed by retesting 4 months after the end of treatment.

Participants visited the hospital three times. The first meeting included providing information about the study, obtaining informed consent signatures, testing cognitive function (pretest) and training to apply tDCS treatment. The second meeting was at the end of the 4-month tDCS treatment and included a new cognitive assessment (posttest). The third meeting was 4 months after the tDCS treatment had ended.

After enrollment, the participants underwent a battery of cognitive tests. Then both the participants and their caregivers were trained by the psychiatrist in how to use the tDCS equipment. After training, the participant and the caregiver tested the equipment in front of the researcher to ensure that they were able to use the device. The project leader made a home visit to the participants within 4 days after the study commenced; another 2 home visits and 3 phone calls were conducted during the 4-month period to check for tDCS feasibility and side effects. The tDCS Adverse Effects Questionnaire was used to assess side effects (Brunoni et al., 2011).

Home-based transcranial direct current stimulation

Active tDCS at 2 mA was applied via surface-based electrodes (round shaped, 4.5 cm in diameter) with saline-soaked sponges daily over a 4-month period. The device used was a Sooma tDCS stimulator. The anode electrode was placed over the left temporal lobe (T7 according to the 10–20 EEG system), and the cathode electrode was placed over the right dorsolateral prefrontal cortex (F4 according to the 10–20 EEG system). A cap from the manufacturer was used to fix the electrodes, -the location of the electrodes was marked by the researchers, and a hole was cut in the cap to insert the electrodes. The participants and their caregivers were trained in placing the cap correctly on the scalp. The

cable attachment points on the cap were labeled "RED" and "BLACK" to ensure that the cables were properly placed. Upon a press of the start button, the current ramped up to 2 mA during the first 30 seconds, remained at 2 mA for 29 minutes and then automatically ramped down to 0 mA during the last 30 seconds. The usage log was automatically stored and was checked at the home visits and at posttest. The participants were instructed to stay awake and sit in a chair during stimulation. No further instructions were given regarding activity, with the rationale that additional limitations could make the procedure overwhelming and less feasible for the patients.

Cognitive assessment

The cognitive test battery included the Mini Mental State Examination (MMSE), Clock Drawing Test, Trail Making Test A and B (TMT A & B) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The MMSE and the Clock Drawing Test are cognitive tests frequently used screen for dementia and, together with TMT A & B, are carried out in the primary health care unit in Norway in the first stage of dementia evaluation. RBANS is a neuropsychological test battery normed by age (Randolph et al., 1998) . This test battery consists of 10 subtests, covering the domains of immediate verbal memory, visuospatial/constructional function, language ability, attention, and delayed visual and verbal memory. To reduce test-retest effects, two parallel versions were administered. RBANS has high specificity (82%) and sensitivity (98%) for the detection of Alzheimer's disease, with test-retest reliability between 0.81 and 0.94 (Duff et al., 2008).

A licensed psychologist conducted the cognitive testing.

Statistical analysis

IBM Statistical Package for the Social Science, version 26 software (SPSS Inc., Chicago, Illinois, USA) was applied in the statistical analysis. Visual inspections of P-P plots and Kolmogorov–Smirnov tests were used to test if the data were normally distributed. For normally distributed variables, paired samples t tests were applied; the Friedman test was used for nonnormally distributed variables. P values <.05 were considered significant.

Results

A total of 8 participants were included in the study. The characteristics of the participants are presented in Table 1. One participant withdrew from the study after three months and reported that she was tired of using the tDCS stimulator, this participant was the only one with moderate stage of AD. In total, 7 participants were included in the final analysis. Dementia stage of AD for each participant, number of sessions and number of skipped sessions is presented in Table 2. All participants were asked repeatedly about side effects based on the tDCS Adverse Effect Questionnaire, but none of the participants reported side effects apart from a slight tingling sensation in the area surrounding the electrodes during the 30-minute treatment. This was not described as painful or as something that made the participants want to end the treatment. Two of the participants managed to put on the cap without assistance from their spouse, while the procedure was administered by the spouse for the other participants. All participants used cholinesterase inhibitor drugs during the 8-month study period.

Table 1. Patient characteristics.

Variable	n
Sex, male	4 (50%)
Age, mean	75 (65–81)
Marital status, married	8 (100%)
Education, years	12.9 (8–25)
Cholinesterase inhibitor	8 (100%)
Years since first symptoms	4.4 (2–8)
Years since diagnosis	2.5 (1–5)

Note: *The values in parenthesis are ranges unless otherwise specified.*

Table 2. Stage of Alzheimers disease including MMSE pre-treatment, number of completed and skipped treatment sessions .

Participant number	AD stage	Number of seesions (skipped)	MMSE pre-treatment
1	Mild	118 (5)	19
2	Mild	115 (7)	22
3	Moderate	55 (6)	16[*]
4	Mild	120 (3)	28
5	Mild	114 (9)	23
6	Mild	117 (6)	25
7	Mild	112 (8)	20
8	MIld	118 (3)	26

[*] *The participant had MMSE <17, but was allowed to participate after an assessment*

The participants and their spouses reported that the treatment was not stressful or tiresome, except for one participant who withdrew after three months. The tolerability and feasibility of the 4-month treatment was therefore regarded as good.

The overall results of the treatment are presented in Table 3. The Friedman test failed to find any significant changes over the eight months on MMSE scores (X^2 (2) = 3.630, p = 0.163), TMT A or B scores (A: X^2 (2) = 0.857, p = 0.66; B: X^2 (2) = 4.80, p = 0.91), clock drawing test scores (X^2 (2) = 2.00, p = 0.36),or on immediate recall (X^2 (2) = 0.51, p = 0.77), attention (X^2 (2) = 2.81, p = 0.24), verbal (X^2 (2) = 2.38, p = 0.30), visuospatial (X^2 (2) = 1.46, p = 0.48), or delayed recall (X^2 (2) = 0.42, p = 0.80) abilities.

Thus, there was no significant improvement in scores on the neuropsychological tests by the end of the treatment period, even if a small non-significant improvement in all tests applied except for the test of visuospatial abilities. The number of participants that improved in scores on the neuropsychological tests during the treatment period and 4 months after the end of treatment is shown in Table 4.

Discussion

In this study involving patients with Alzheimer's disease, a 4-month long daily home-based tDCS treatment was shown to be feasible and well tolerated. Apart from a tingling sensation on the electrode sites, no side effects were reported. A small nonsignificant improvement in nearly all the measured

Table 3. Results after 4 months of treatment and 4 months after the end of treatment.

	Pretest mean (SD)	Posttest	4 months after Posttest
MMSEa	23.3 (3.3)	24.3 (4.4)	22.1 (4.6)
Clock drawing test	4.4 (1.5)	4.6 (1.1)	4.6 (1.1)
TMT A "'	70.0 (29.1)	68.4 (40.2)	73.7 (54.9)
TMT B	140 (95.2)	93.2 (41.1)	132.4 (60.3)
RBANS index	348.3 (69)	352.9 (103)	342.7 (79)
RBANS raw score	56.3 (18.6)	60.1 (25.7)	55.9 (19.7)
Immediate recall	64.3 (16.2)	66.3 (19.2)	65.3 (15.4)
Raw score	*29.7 (7.6)*	*30.3 (9.3)*	*29.9 (7.3)*
Visuospatial	94 (18.0)	84.6 (27.9)	87.0 (25.0)
Raw score	*33.6 (5.0)*	*30.4 (9.3)*	*31.1 (8.1)*
Languagea**	68.7 (9.9)	74.0 (21.0)	69.4 (10.6)
Attention	70.0 (26.0)	72.9 (25.2)	66.0 (27.9)
Raw score	*33.9 (12.7)*	*35.1 (12.7)*	*32.1 (14.8)*
Delayed memory	51.3 (34.2)	55.1 (25.3)	55.0 (23.2)
Raw score	*22.7 (12.9)*	*22.9 (13.5)*	*22.6 (12.4)*

a*MMSE: maximum score 30 point ** Clock drawing test: lowest score is 0 and maximum score is 5., *** TMT A & B are displayed in seconds.Immediate recall, visuospatial function, language, attention, and delayed recall are from the repeatable battery for the assessment of neuropsychological status (RBANS) and are index scores (normalized mean is 100, SD = 15).*

Table 4. Number of participants with improvement in neuropsychological test scores.

	Pretest to posttest	Posttest to 4 months after Posttest
MMSE	5 (0/2)[a]	1 (1/5)
Clock drawing	1 (6/0)	0 (7/0)
TMT A	5 (0/1)	4 (0/3)
TMT B	4 (0/3)	0 (2/5)
Immediate recall	4 (0/3)	3 (0/4)
Visuospatial	3 (0/4)	5 (1/1)
Language	5 (1/1)	3 (0/4)
Delayed memory	5 (1/1)	3 (0/4)

Note*: The data present the number of participants showing improvements. Improvement is defined as positive changes either from pretest to posttest 1 or from posttest 1 to posttest 2. [a]Numbers in parentheses indicate ("no changes"/"worsened").*

areas was observed, followed by a small decline 4 months after the end of treatment, but it is not possible to draw any conclusion about effect in this study

The equipment used in home-based tDCS is not technically complicated, but it involves some procedural steps that can be challenging for people with dementia. However, with support from a spouse, our study has shown that home-based tDCS is feasible. Two patients managed to administer the treatment themselves, but our overall impression is that this patient group must rely on either a spouse or a daily visit from a health care worker to ensure a proper treatment procedure. The patient who dropped out of the study had the lowest MMSE and RBANS scores in the sample.

Most studies on tDCS have used a short treatment period of 5–10 days, and few side effects have been reported (Boggio et al., 2012; Bystad et al., 2016; Cotelli et al., 2014).However, it is not obvious how these observations will apply to long-term home-based treatment; therefore, mild side effects reported in our study is intriguing and is consistent with another home-based study on patients with dementia (Im et al., 2019). Home-based tDCS has also been used to treat other conditions, such as depression and pain, and the same low frequency of side effects has been reported in these studies (Alonzo et al., 2019; Brietzke et al., 2020).

The improvement in participants' scores on the neuropsychological tests was not significant. This study was a pilot study with few participants, and the improvement could have been due to coincidence or a placebo effect. However, placebo effects in dementia are relatively low (Benedetti et al., 2011). In addition, it is not possible to rule out a type II error due to the small number of participants. Alzheimer's disease progressively advances but some patients remain stable for up to a year or longer. The improvements in neuropsychological test scores after 4 months of treatment in this study, although not significant, are promising and supported by another home-based study (Im et al., 2019). In a 6-month RCT (n = 18) Im and colleagues used active and sham home-based tDCS over the DLPFC and reported small but significant improvements in MMSE and language function, but not in delayed recall. A case study using home-based tDCS treatment over the left temporal lobe for a 8 month period reported stable cognitive function in the study period and a 23% improvement in delayed recall (Bystad et al., 2017).

Research on tDCS is complicated to interpret due to lack of consensus on electrode placement, duration of treatment and which cognitive tests to administer (Gonzalez et al., 2018). Most studies on Alzheimer's disease have used either anodal stimulation of the DLPFC (Cotelli et al., 2014; Khedr et al., 2014; Suemoto et al., 2014) or the left temporal lobe (Boggio et al., 2012; Bystad et al., 2016; Ferrucci et al., 2008). In our study, anodal stimulation of the temporal lobe was used due to its role in memory functions. We also wanted to apply the same procedure that was used in a home-based 8-month case study (Bystad et al., 2017). When evaluating the effect of tDCS it is important to not only consider the effect of the chosen "active" electrode (here anodal tDCS), but also evaluate the influence of the reference electrode (here cathodal tDCS). Older adults in general, and especially patients with Alzheimer's disease, have a more widespread activation pattern when executing memory tasks, involving both the left and the right hemisphere (Grady et al., 2003;; Pariente et al., 2005). In addition, the right DLPFC is involved in tasks such as inhibitory control, with anodal tDCS in particular shown to improve this function (Schroeder et al., 2020). By inhibiting important cognitive functions in the right frontal areas in Alzheimer's patients, the cognitive gains of anodal tDCS over the left cortices may be hampered. Conventional tDCS causes bidirectional stimulation with current flowing between the two hemispheres, not concentrated only beneath the anode electrode placed on the area of interest. To focalize current to the area of interest, high definition (HD)-tDCS is an option (Datta et al., 2009). Usually, five small electrodes are placed in a ring formation, with the polarity of the middle electrode determining the direction of the current (Villamar et al., 2013). Compared to conventional tDCS, high-definition tDCS devices provide higher precision during stimulation. However, HD-tDCS devices today are more complicated to administer than conventional tDCS (e.g., low impedance and correct placement for all five electrodes must be ensured). If the

use of HD-tDCS devices is facilitated in the future, HD in home studies with multiple tDCS sessions may be an important research area for patients with cognitive decline.

We used a 30-minute treatment period. The duration of tDCS stimulation is under debate. Some authors argue that 20 minutes of stimulation should be used, instead of 30 minutes. Monte-Silva and colleagues found that tDCS sessions exceeding 26 minutes may lead to inhibitory effects rather than excitatory effects (Monte-Silva et al., 2013). This is caused by an overabundance of calcium that impairs neuroplasticity.

Some studies have combined cognitive training and tDCS (Boggio et al., 2009; Cotelli et al., 2014). In a review by Gonzales and colleagues no conclusive advantage in combining the two was found (Gonzalez et al., 2018). As in tDCS literature in general, these studies are heterogeneous regarding stimulation site, electrode size, task given and variation among participants, among others. In a recent study by Andrade and colleagues, Alzheimer's patients receiving cognitive stimulation combined with tDCS showed delayed cognitive decline and changes in EEG activity compared to patients receiving cognitive training and sham tDCS. The results showed that individuals earlier in the disease course had greater changes in the EEG analysis before and after treatment.(Andrade et al., 2022). The use of EEG and perhaps other biomarkers could provide information to why some individuals respond better to tDCS than others.

Home-based treatment for Alzheimer's disease is feasible and tolerated. To establish whether the treatment is efficient, further studies should be conducted with even longer treatment durations, and 20-minute session periods could also be considered. Other studies could investigate which stage of the disease the treatment should start at, whether it is more efficient than the current dementia drugs and if there are patient characteristics that could predict better outcomes (e.g., genetics, age, duration of the disease, level of cognitive decline at inclusion).

Strength and limitations

This study has several limitations. The sample size was small, and it was an open-label study; thus, it was not designed to detect significant effects of the treatment. Rare side effects could be missed due to the size of the study, but as pointed out in the discussion, only minor side effects have been reported in other, larger tDCS studies. The participants reported assessing different activities during the stimulation period. Some watched the news, some ate breakfast and others reported resting. The tasks during tDCS was not controlled, being a limitation of our study. A specific task could have made the brain state more similar across patients and cognitive task during the stimulation may improve the cognitive effect of tDCS.

The patients had participated in a short tDCS study in a laboratory more than 4 months prior to inclusion in the present study. It is not likely that this previous tDCS stimulation would influence the results, but the participants could be especially motivated to participate in this kind of study.

The strengths of the study are a relatively long treatment period followed by a 4-month follow-up, close monitoring for side effects and the use of an age-normed neuropsychological test battery to assess a variety of cognitive functions.

Conclusion

A 4-month home-based tDCS treatment of 8 patients with Alzheimer's disease revealed that the treatment method was feasible and well tolerated. We did not find any significant improvements in neuropsychological test scores during the treatment period. Further studies with greater numbers of participants and longer treatment periods should be conducted.

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Authors`contributions

OKG, IDR, PMA and MB planned the study. IDR and OKG trained the patients and spouses. IDR performed neuropsychological testing. All authors contributed to analysis. IDR and OKG made the first draft of the manuscript and all authors have approved the final version of the manuscript.

Ethical approval and consent to participate

All the participants were able to give consent to participate in the study and signed a written consent form. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Regional Committee for Medical and Health Research Ethics (2018/1662). The study is registered at Clinicaltrials.gov (NCT04759092).

Data availability statement

The data is not located on an open server, but could be made available on request to the corresponding author.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

Alexopoulos, G. S., Abrams, R. C., Young, R. C., & Shamoian, C. A. (1988). Cornell scale for depression in dementia. *Biological Psychiatry*, *23*(3), 271–284. https://doi.org/10.1016/0006-3223(88)90038-8

Alonzo, A., Fong, J., Ball, N., Martin, D., Chand, N., & Loo, C. (2019). Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. *Journal of Affective Disorders*, *252*, 475–483. https://doi.org/10.1016/j.jad.2019.04.041

Andrade, S. M., Machado, D., Silva-Sauerc, L. D., Regis, C. T., Mendes, C., de Araujo, J. S. S., de Araujo, K. D. T., Costa, L. P., Queiroz, M., Leitao, M. M., & Fernandez-Calvo, B. (2022). Effects of multisite anodal transcranial direct current stimulation combined with cognitive stimulation in patients with Alzheimer's disease and its neurophysiological correlates: A double-blind randomized clinical trial. *Neurophysiologie Clinique*, *52*(2), 117–127. https://doi.org/10.1016/j.neucli.2022.02.003

Benedetti, F., Carlino, E., & Pollo, A. (2011). How placebos change the patient's brain. *Neuropsychopharmacology*, *36*(1), 339–354. https://doi.org/10.1038/npp.2010.81

Bikson, M., Grossman, P., Thomas, C., Zannou, A. L., Jiang, J., Adnan, T., Mourdoukoutas, A. P., Kronberg, G., Truong, D., Boggio, P., Brunoni, A. R., Charvet, L., Fregni, F., Fritsch, B., Gillick, B., Hamilton, R. H., Hampstead, B. M., Jankord, R., Kirton, A., … Woods, A. J. (2016). Safety of transcranial direct current stimulation: Evidence based update 2016. *Brain Stimulation*, *9*(5), 641–661. https://doi.org/10.1016/j.brs.2016.06.004

Boggio, P. S., Khoury, L. P., Martins, D. C., Martins, O. E., de Macedo, E. C., & Fregni, F. (2009). Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *80*(4), 444–447. https://doi.org/10.1136/jnnp.2007.141853

Boggio, P. S., Ferrucci, R., Mameli, F., Martins, D., Martins, O., Vergari, M., Tadini, L., Scarpini, E., Fregni, F., & Priori, A. (2012). Prolonged visual memory enhancement after direct current stimulation in Alzheimer's disease. *Brain Stimulation*, *5*(3), 223–230. https://doi.org/10.1016/j.brs.2011.06.006

Brietzke, A. P., Zortea, M., Carvalho, F., Sanches, P. R. S., Silva, D. P., Torres, I. L. D., Fregni, F., & Caumo, W. (2020). Large treatment effect with extended home-based transcranial direct current stimulation over dorsolateral prefrontal cortex in fibromyalgia: A proof of concept sham-randomized clinical study. *Journal of Pain*, *21*(1–2), 212–224. https://doi.org/10.1016/j.jpain.2019.06.013

Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., & Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *International Journal of Neuropsychopharmacology*, *14*(8), 1133–1145. https://doi.org/10.1017/S1461145710001690

Bystad, M., Gronli, O., Rasmussen, I. D., Gundersen, N., Nordvang, L., Wang-Iversen, H., & Aslaksen, P. M. (2016). Transcranial direct current stimulation as a memory enhancer in patients with Alzheimer's disease: A randomized, placebo-controlled trial. *Alzheimer's Research & Therapy*, *8*(1), 13. https://doi.org/10.1186/s13195-016-0180-3

Bystad, M., Rasmussen, I. D., Gronli, O., & Aslaksen, P. M. (2017). Can 8 months of daily tDCS application slow the cognitive decline in Alzheimer's disease? A case study. *Neurocase*, *23*(2), 146–148. https://doi.org/10.1080/13554794.2017.1325911

Cai, M., Guo, Z., Xing, G., Peng, H., Zhou, L., Chen, H., McClure, M. A., He, L., Xiong, L., He, B., Du, F., & Mu, Q. (2019). Transcranial direct current stimulation improves cognitive function in mild to moderate Alzheimer disease: A meta-analysis. *Alzheimer Disease & Associated Disorders*, *33*(2), 170–178. https://doi.org/10.1097/WAD.0000000000000304

Charvet, L. E., Kasschau, M., Datta, A., Knotkova, H., Stevens, M. C., Alonzo, A., Loo, C., Krull, K. R., & Bikson, M. (2015). Remotely-supervised transcranial direct current stimulation (tDCS) for clinical trials: Guidelines for technology and protocols. *Frontiers in Systems Neuroscience*, *9*, 26. https://doi.org/10.3389/fnsys.2015.00026

Clement, C., Selman, L. E., Kehoe, P. G., Howden, B., Lane, J. A., & Horwood, J. (2019). Challenges to and facilitators of recruitment to an Alzheimer's disease clinical trial: A qualitative interview study. *Journal of Alzheimer's Disease*, *69*(4), 1067–1075. https://doi.org/10.3233/JAD-190146

Cotelli, M., Manenti, R., Brambilla, M., Petesi, M., Rosini, S., Ferrari, C., Zanetti, O., & Miniussi, C. (2014). Anodal tDCS during face-name associations memory training in Alzheimer's patients. *Frontiers in Aging Neuroscience*, *6*, 38. https://doi.org/10.3389/fnagi.2014.00038

Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D., & Bikson, M. (2009). Gyri-precise head model of transcranial direct current stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain Stimulation*, *2*(4), 201–207, 207 e201. https://doi.org/10.1016/j.brs.2009.03.005

Dickerson, B. C., & Sperling, R. A. (2008). Functional abnormalities of the medial temporal lobe memory system in mild cognitive impairment and Alzheimer's disease: Insights from functional MRI studies. *Neuropsychologia*, *46*(6), 1624–1635.https://doi.org/10.1016/j.neuropsychologia.2007.11.030

Duff, K., Humphreys Clark, J. D., O'Bryant, S. E., Mold, J. W., Schiffer, R. B., & Sutker, P. B. (2008). Utility of the RBANS in detecting cognitive impairment associated with Alzheimer's disease: Sensitivity, specificity, and positive and negative predictive powers. *Archives of Clinical Neuropsychology*, *23*(5), 603–612. https://doi.org/10.1016/j.acn.2008.06.004

Ferrucci, R., Mameli, F., Guidi, I., Mrakic-Sposta, S., Vergari, M., Marceglia, S., Cogiamanian, F., Barbieri, S., Scarpini, E., & Priori, A. (2008). Transcranial direct current stimulation improves recognition memory in Alzheimer disease. *Neurology*, *71*(7), 493–498. https://doi.org/10.1212/01.wnl.0000317060.43722.a3

Frisoni, G. B., Fox, N. C., Jack, C. R., Jr., Scheltens, P., & Thompson, P. M. (2010). The clinical use of structural MRI in Alzheimer disease. *Nature Reviews Neurology*, *6*(2), 67–77. https://doi.org/10.1038/nrneurol.2009.215

Gonzalez, P. C., Fong, K. N. K., Chung, R. C. K., Ting, K. H., Law, L. L. F., & Brown, T. (2018). Can transcranial direct-current stimulation alone or combined with cognitive training be used as a clinical intervention to improve cognitive functioning in persons with mild cognitive impairment and dementia? A systematic review and meta-analysis. *Frontiers in Human Neuroscience*, 12. https://ARTN41610.3389/fnhum.2018.0041612

Grady C L, McIntosh A R and Craik F IM. (2003). Age-related differences in the functional connectivity of the hippocampus during memory encoding. Hippocampus, 13(5), 572–586. 10.1002/hipo.10114

Grill, J. D., & Karlawish, J. (2010). Addressing the challenges to successful recruitment and retention in Alzheimer's disease clinical trials. *Alzheimer's Research & Therapy*, *2*(6), 34. https://doi.org/10.1186/alzrt58

Hagenacker, T., Bude, V., Naegel, S., Holle, D., Katsarava, Z., Diener, H. C., & Obermann, M. (2014). Patient-conducted anodal transcranial direct current stimulation of the motor cortex alleviates pain in trigeminal neuralgia. *The Journal of Headache and Pain*, *15*, 78. https://doi.org/10.1186/1129-2377-15-78

Hansen, N. (2012). Action mechanisms of transcranial direct current stimulation in Alzheimer's disease and memory loss. *Frontiers in Psychiatry*, *3*, 48. https://doi.org/10.3389/fpsyt.2012.00048

Hsu, W. Y., Ku, Y., Zanto, T. P., & Gazzaley, A. (2015). Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: A systematic review and meta-analysis. *Neurobiology of Aging*, *36*(8), 2348–2359. https://doi.org/10.1016/j.neurobiolaging.2015.04.016

Im, J. J., Jeong, H., Bikson, M., Woods, A. J., Unal, G., Oh, J. K., Na, S., Park, J. S., Knotkova, H., Song, I. U., & Chung, Y. A. (2019). Effects of 6-month at-home transcranial direct current stimulation on cognition and cerebral glucose metabolism in Alzheimer's disease. *Brain Stimulation*, *12*(5), 1222–1228. https://doi.org/10.1016/j.brs.2019.06.003

Khedr, E. M., Gamal, N. F., El-Fetoh, N. A., Khalifa, H., Ahmed, E. M., Ali, A. M., Noaman, M., El-Baki, A. A., & Karim, A. A. (2014). A double-blind randomized clinical trial on the efficacy of cortical direct current stimulation for the treatment of Alzheimer's disease. *Frontiers in Aging Neuroscience*, *6*, 275. https://doi.org/10.3389/fnagi.2014.00275

Koch, G., Di Lorenzo, F., Bonni, S., Ponzo, V., Caltagirone, C., & Martorana, A. (2012). Impaired LTP- but not LTD-like cortical plasticity in Alzheimer's disease patients. *Journal of Alzheimer's Disease*, *31*(3), 593–599. https://doi.org/10.3233/JAD-2012-120532

Kumar, S., Zomorrodi, R., Ghazala, Z., Goodman, M. S., Blumberger, D. M., Cheam, A., Fischer, C., Daskalakis, Z. J., Mulsant, B. H., Pollock, B. G., & Rajji, T. K. (2017). Extent of dorsolateral prefrontal cortex plasticity and its association with working memory in patients with Alzheimer disease. *JAMA Psychiatry*, *74*(12), 1266–1274. https://doi.org/10.1001/jamapsychiatry.2017.3292

Liebetanz, D., Nitsche, M. A., Tergau, F., & Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain*, *125*, 2238–2247. doi:10.1093/brain/awf238.

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R. C., Morris, J. C., Rossor, M. N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S., & Phelps, C. H. (2011). The diagnosis of dementia due to *Alzheimer*'s disease: Recommendations from the national institute on aging-*Alzheimer*'s Association workgroups on diagnostic guidelines for *Alzheimer*'s disease. *Alzheimer's & Dementia*, *7*(3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005

Medeiros, L. F., de Souza, I. C., Vidor, L. P., de Souza, A., Deitos, A., Volz, M. S., Fregni, F., Caumo, W., & Torres, I. L. (2012). Neurobiological effects of transcranial direct current stimulation: A review. *Frontiers in Psychiatry*, *3*, 110. https://doi.org/10.3389/fpsyt.2012.00110

Monte-Silva, K., Kuo, M. F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain Stimulation*, *6*(3), 424–432. https://doi.org/10.1016/j.brs.2012.04.011

Mosconi, L., Brys, M., Glodzik-Sobanska, L., De Santi, S., Rusinek, H., & de Leon, M. J. (2007). Early detection of Alzheimer's disease using neuroimaging. *Experimental Gerontology*, *42*(1–2), 129–138. https://doi.org/10.1016/j.exger.2006.05.016

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., Henning, S., Tergau, F., & Paulus, W. (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *The Journal of Physiology*, *553*(Pt 1), 293–301. https://doi.org/10.1113/jphysiol.2003.049916

Nitsche, M. A., Liebetanz, D., Lang, N., Antal, A., Tergau, F., & Paulus, W. (2003). Safety criteria for transcranial direct current stimulation (tDCS) in humans. *Clinical Neurophysiology*, *114*(11), 2220–2222. https://doi.org/10.1016/s1388-2457(03)00235-9. author reply 2222-2223.

Pariente J *et al* . (2005). Alzheimer's patients engage an alternative network during a memory task. Ann Neurol, 58(6), 870–879. 10.1002/ana.20653

Rajji, T. K. (2019). Transcranial magnetic and electrical stimulation in Alzheimer's disease and mild cognitive impairment: A review of randomized controlled trials. *Clinical Pharmacology & Therapeutics*, *106*(4), 776–780. https://doi.org/10.1002/cpt.1574

Randolph, C., Tierney, M. C., Mohr, E., & Chase, T. N. (1998). The repeatable battery for the assessment of neuropsychological status (RBANS): Preliminary clinical validity. *Journal of Clinical and Experimental Neuropsychology*, *20*(3), 310–319. https://doi.org/10.1076/jcen.20.3.310.823

Rasmussen, I. D., Boayue, N. M., Mittner, M., Bystad, M., Gronli, O. K., Vangberg, T. R., Csifcsak, G., Aslaksen, P. M., & Peter, J. (2021). High-definition transcranial direct current stimulation improves delayed memory in Alzheimer's disease patients: A pilot study using computational modeling to optimize electrode position. *Journal of Alzheimer's Disease*, *83*(2), 753–769. https://doi.org/10.3233/JAD-210378

Remy, F., Mirrashed, F., Campbell, B., & Richter, W. (2005). Verbal episodic memory impairment in Alzheimer's disease: A combined structural and functional MRI study. *Neuroimage*, *25*(1), 253–266.https://doi.org/10.1016/j.neuroimage.2004.10.045

Schroeder P A, Artemenko C, Cipora K and Svaldi J. (2020). Regional specificity of cathodal transcranial direct current stimulation (tDCS) effects on spatial-numerical associations: Comparison of four stimulation sites. J Neurosci Res, 98(4), 655–667. 10.1002/jnr.24559

Stagg, C. J., Best, J. G., Stephenson, M. C., O'Shea, J., Wylezinska, M., Kincses, Z. T., Morris, P. G., Matthews, P. M., & Johansen-Berg, H. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *Journal of Neuroscience*, *29*(16), 5202–5206. https://doi.org/10.1523/JNEUROSCI.4432-08.2009

Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *The Neuroscientist*, *17*(1), 37–53. https://doi.org/10.1177/1073858410386614

Suemoto, C. K., Apolinario, D., Nakamura-Palacios, E. M., Lopes, L., Leite, R. E. P., Sales, M. C., Nitrini, R., Brucki, S. M., Morillo, L. S., Magaldi, R. M., & Fregni, F. (2014). Effects of a non-focal plasticity protocol on apathy in moderate Alzheimer's disease: A randomized, double-blind, sham-controlled trial. *Brain Stimulation*, *7*(2), 308–313. https://doi.org/10.1016/j.brs.2013.10.003

Valiengo, L., Bensenor, I. M., Goulart, A. C., de Oliveira, J. F., Zanao, T. A., Boggio, P. S., Lotufo, P. A., Fregni, F., & Brunoni, A. R. (2013). The sertraline versus electrical current therapy for treating depression clinical study (select-TDCS): Results of the crossover and follow-up phases. *Depression and Anxiety*, *30*(7), 646–653. https://doi.org/10.1002/da.22079

Villamar, M. F., Volz, M. S., Bikson, M., Datta, A., Dasilva, A. F., & Fregni, F. (2013). Technique and considerations in the use of 4x1 ring high-definition transcranial direct current stimulation (HD-tDCS). *J Vis Exp*(77), e50309. https://doi.org/10.3791/50309