Long- term improvement in Alzheimer's Disease with Transcranial Direct Current Stimulation

Anu Aggarwal, member IEEE
Department of Electrical and Computer Engineering
University of Illinois Urbana Champaign

Abstract. The goal of this work was to integrate results from clinical trials related to transcranial direct current stimulation (tDCS) treatment of Alzheimer's disease (AD) into a machine learning model of the disease to understand its impact on disease progression over a decade. The ***main contributions*** of this work are- firstly, extension of otherwise sparse clinical data for tDCS stimulation in AD patients to predict patient outcomes over a decade. Secondly, it provides evidence of long-term improvement in AD with tDCS. Thirdly, it calculates an optimal tDCS regimen for improvement in cognitive function for patients with AD. This paper integrates data from an emerging field of research (tDCS treatment) into general guidelines for best stimulation practices and potential outcomes which can be replicated to other diseases and treatments.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60-80% of cases in the US [1]. It is a progressive neurodegenerative disorder that primarily affects memory such that it adversely impacts the activities of daily living. Despite ongoing research, there is no definitive cure for the disease, leading to high end-of-life nursing health care costs for the affected individuals. AD is characterized by abnormal beta-amyloid plaques and tau tangle accumulation in the brain. As the disease advances, there is reduction in brain volume due to fibrosis after the abnormal protein deposits. Thus, measuring brain volume is one of the ways to determine disease progression.

There is no definitive but several provisional treatments for the disease. Among other things, transcranial direct current stimulation (tDCS) is being used as a provisional treatment. However, documented use of this treatment [5]-[21] is limited in duration and number of patients due to which it is difficult to assess its impact over a longer duration. Over the short duration of these studies, a significant increase in cognitive scores has been observed in treatment group as compared to sham, as determined by the Mini Mental State Exam (MMSE) scores. But there is no data on the impact of tDCS on brain volume and brain health or long-term impact on cognitive scores. Work presented here extrapolates the cognitive score data from the studies to a period of a decade and to brain volume and brain health using the Alzheimer's Disease Progression Model (ADPM).

2. Background

The ADPM uses data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) [22] for 100 patients and processes it using differential equations and reinforcement learning to estimate changes in brain health and cognitive scores over a 10-year period [2]. While the ADPM models disease progression over a period, it does not study the impact of tDCS. The ADPM represents brain as a graph, $G_s = (V, E)$, where a node $v \in V$ indicates brain regions – the hippocampus (HC) and the pre-frontal cortex (PFC). An edge $e \in E$ indicates a tract connecting the regions. The brain region volume for the PFC and the HC of Alzheimer's patients was taken from the ADNI and normalized to lie between 3.5-5.5. The latter follows patients over a 10-year timespan using MRI to determine the brain region volume. It also tracks the cognitive scores using MMSE over a similar period. In addition, the model parameters are calculated from the demographic features of the population. The model defines a relationship between brain region size $X_v(t)$, brain activity $Y_v(t)$, and the information processed by each region of the brain $I_v(t)$ as follows:

$$Y_v(t) = \gamma \frac{I_v(t)}{X_v(t)} \; \forall v \in V \tag{1}$$

where γ is a constant. Furthermore, the ADPM relates brain region volume with amyloid deposition and brain activity as:

$$\frac{dX_v(t)}{dt} = -\alpha_1 D_v(t) - \alpha_2 Y_v(t) \tag{2}$$

where α_1 and α_2 are constants and $D_v(t)$ is the instantaneous amyloid accumulation in the brain region v at time t. The ADPM estimates the cognitive score, $C(t)$ by summing $I_v(t)$ across the two brain regions:

$$C(t) = \sum_{v \in V} I_v(t). \tag{3}$$

$C(t)$ is the MMSE score normalized to lie between 0-10.

The MMSE [3] is a clinical exam in which patients are administered an 11-question questionnaire. The questions are designed to measure cognitive functions such as orientation, registration, attention, recall and language. Based on the patient response, their cognitive score is calculated. It varies from 0 to 30, with 30 being the best possible cognitive level. It is

used in the evaluation of mental health. As mentioned earlier, the MMSE scores are normalized to lie between 0-10 in the ADPM.

The goal of tDCS treatment is to enhance cognitive function by running a weak electrical current through two electrodes placed on a patient's scalp. The current applied via anodal tDCS depolarizes neurons' resting membrane potential, thereby increasing excitability. The electrodes can be placed such that a specific brain area can be stimulated [4]. The modification of the ADPM in the current work, models stimulation of either the HC, the PFC or both by applying different amounts of tDCS.

3. Methods

The ADPM was modified to integrate the impact of tDCS on cognitive scores, as estimated from seventeen prior studies [5]-[21]. In these studies, 2mA current stimulation was applied for 10 days to 8 months, once a day for 20-30 minutes a day. The progress in cognitive score (MMSE) was monitored during the treatment period in all the studies and beyond the treatment period in some of the studies. However, no study observed the change in brain pathology using MRI. Using data from these studies, the ADPM was modified to predict disease progression in terms of change in brain volume in Alzheimer's disease over ten year period.

3.1 Modification Applied to the Model

We modified the ADPM to introduce the effect of tDCS on a patient as improvement in cognitive score for a given current applied based on data from priors (Fig. 1). For this, a new stimulation parameter, ΔI_{stim} was added to the model. In this updated version of the ADPM, a new version of $I_v(t)$ called $\hat{I}_v(t)$ is defined as:

$$\hat{I}_v(t) = I_v(t) - \Delta I_{stim} \qquad (4)$$

$\hat{I}_v(t)$ replaces all instances of $I_v(t)$ in equations (1) and (3) in the updated ADPM. Since $Y_v(t)$ will change due to this addition, the impact will propagate to calculation of brain volume in (2). The brain stimulation with tDCS (as determined from priors) alters information processed by each brain region. The effectiveness of tDCS stimulation on brain health is measured by change in the HC and the PFC volume over ten years using the ADPM. An increase in brain volume indicates improvement in brain function and a decrease in volume indicates reduction in brain function. Multiple values of ΔI_{stim} were surveyed to examine the effect of tDCS on brain health over the decade. Several experiments were done as follows:

To determine the level of tDCS stimulation required for a patient, a range of ΔI_{stim} between 0.1 to 5 was applied to the model. This corresponds to a range of MMSE score increase between 0.3-15 (as the cognitive score is normalized to lie within 0-10 in the ADPM instead of the actual value between 0-30).

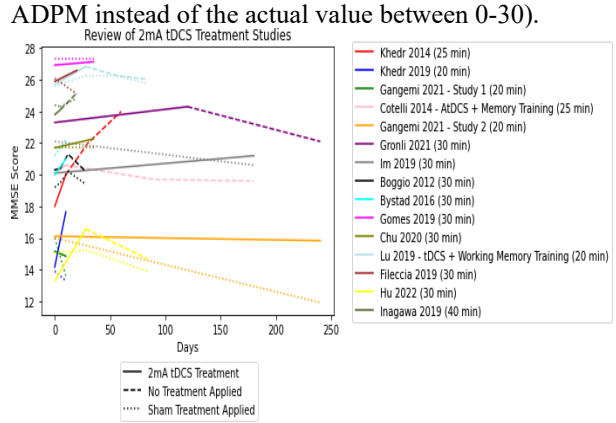

Fig. 1 The effect of tDCS stimulation on cognitive scores in Alzheimer's patients from priors [7-20]. The graph on the left shows the change in cognitive score for stimulation with 2mA tDCS over the number of days shown. Right column references the study from which the data is taken along with the time for which daily stimulation is applied.

- To determine the region of brain that needs stimulation, it was applied to either the PFC or the HC or both regions. When applying ΔI_{stim} to both regions, the value of ΔI_{stim} applied to each region was halved.
- Stimulating different regions for different periods of time could lead to more optimal results. To explore this further, six stimulation regimens were used:
  - 3years of HC stimulation followed by 3years of PFC and followed by 4years of HC (HC334),
  - 3years of PFC stimulation followed by 3years of HC and followed by 4years of PFC (PFC334),
  - 5years of PFC followed by 5years of HC (PFC5),
  - 5years of HC followed by 5years of PFC (HC5),
  - 2years of alternating HC and PFC stimulation – beginning with
    - HC (HC2)
    - PFC (PFC2)

Last 6 experiments were performed with a ΔI_{stim} value of 0.8, which equates to an MMSE score increase of 2.4 per year. This stimulation was chosen because the stimulation data depicted in Fig. 1 indicates an increase of 2.4 points on the MMSE per year with 2mA for 30 minutes a day for 10days. The change in MMSE score was integrated into the model using the method described above. Upon stimulation, change in brain region volume (HC or PFC) over a period of 1-10 years was studied as an indicator of disease

progression. The results from different stimulation paradigms are shown in the next section.

4. Results

The original ADPM provides projected values for brain volume over 10 years, serving as a baseline to quantify an increase or decrease of region volume. The mean values of the difference in volume between baseline and stimulation results are shown in Fig. 2-Fig. 4.

4.1 PFC and HC Stimulation

The largest changes in PFC or HC volume occur when stimulating only the respective region. Across all time points and levels of stimulation, the PFC volumes increase over baseline when stimulating the PFC, and the HC volumes increase over baseline when stimulating the HC (baseline volume was normalized in the ADPM to lie between 3.5-5.5). Furthermore, the value of ΔI_{stim} largely impacts the rate of volume change. Stimulating the PFC tends to produce a decrease in HC volumes over time, as shown in Fig. 2. In contrast, when HC stimulation is applied, there is a noticeable reduction in PFC volume relative to baseline across all MMSE score improvements (in the range of 124 mm^3 to 1887 mm^3, with higher MMSE score improvements leading to larger decreases).

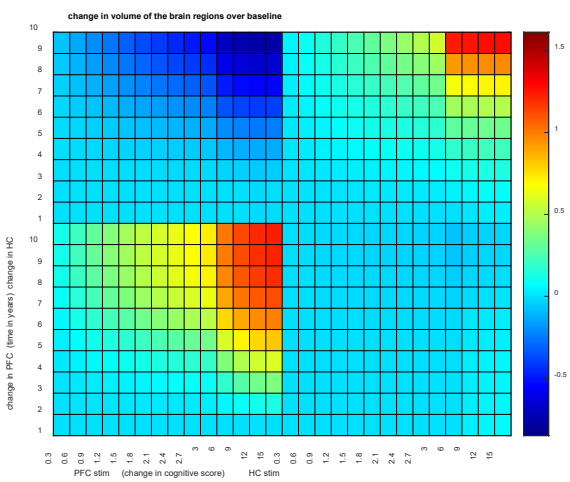

Fig. 2 Showing mean change in HC and PFC volume over a period of 10 years when different current stimulation and corresponding change in MMSE scores was applied over a period of 10years in the ADPM. Change in volume is with respect to baseline results for the same year when patient did not receive any treatment. There is a positive volume change in the PFC or the HC if the stimulation is applied to the same region as opposed to that applied to the other region. HC stimulation does not seem to have a negative impact on the PFC volume, but PFC stimulation has a negative impact on the HC volume.

4.2 Simultaneous PFC and HC Stimulation

For a value of ΔI_{stim}, half of the stimulation is applied to the HC and half to the PFC. In this experiment, the overall trends are similar to those in the first experiment, but differ in magnitude, as seen in Fig. 3. Dual stimulation produces a dampened version of the results of single region stimulation. For example, with a projected cognitive score increase of 0.6 per year, the dual stimulation results in a mean PFC volume increase of 3173.14mm^3 over baseline at year 10, whereas stimulating only the PFC with the same projected cognitive score increase results in an increase of 6054.72 mm^3 in terms of actual (not normalized) volume. All projected cognitive score increases result in an increase in the PFC volume over baseline at the same time for all timesteps. Lower projected cognitive score increases per year result in decreased HC volumes over baseline. By year 10, MMSE score increases of 6 per year (corresponding to ΔI_{stim} of 2.0) or higher are the only ones causing an increase in the HC volume over baseline. The observed results could be because the combined stimulation results in summation of outputs seen with individual region stimulation.

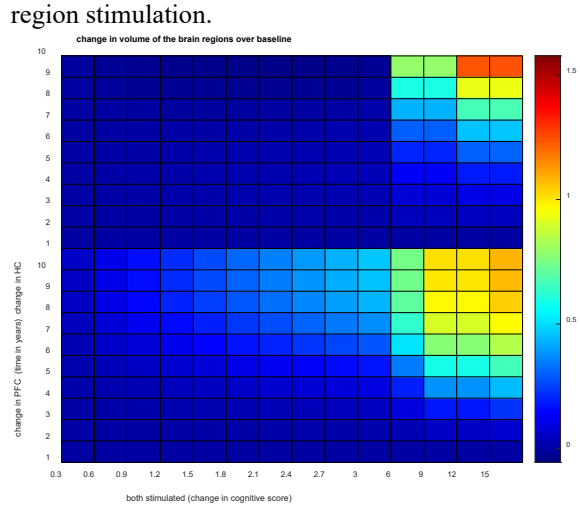

Fig. 3 Mean change in PFC and HC volume over a period of 10 years when different current stimulation and corresponding change in MMSE scores was applied in the ADPM – with half the stimulation applied to HC and the other half to the PFC. Differences are with respect to baseline results at the same year for untreated patients. There is a positive volume change in both the PFC and the HC if the stimulation is applied to both regions but only in the later years and with much higher level than when stimulation is applied to either region alone.

4.3 Alternating PFC and HC Stimulation Over Time

For this experiment, the ΔI_{stim} per year was held at 0.8, as line of best fit for the graph in Fig.1 results in an average MMSE score increase of 2.4 per year. Six different stimulation protocols were used with this ΔI_{stim} as mentioned earlier.

From Fig. 4, it is evident that the maximum change in unnormalized PFC volume at year 10 was 16755 mm^3, which is similar to that of 17502 mm^3 with PFC

stimulation alone. This maximum was achieved in the PFC5 protocol. The dual stimulation (as seen in the previous experiment) for 2.4 projected increase in MMSE score resulted in a maximum PFC volume increase of 10826 mm^3. This indicates that to get the maximum improvement in health of the PFC, the tDCS should be applied to the PFC alone. From the results, it is also evident that for the HC, the maximum unnormalized volume change was 594 mm^3 using the HC5 protocol. For the 2.4 projected MMSE score increase, the maximum change is lower than that from single stimulation (1013 mm^3), but higher than that from dual stimulation (-108 mm^3). Therefore, to attain the maximum HC volume increase, stimulating only the HC seems to be the best option. From the figure, it is also evident that the stimulation protocol that results in the largest increase in PFC volume results in the largest decrease in HC volume. The protocol with the largest increase in HC volume does not decrease, but it attains the smallest increase in PFC volume by year 10. Thus, making it difficult to attain best results for both regions with a single stimulation protocol.

4.4 tDCS to MMSE Prediction Model

The MMSE score increase integrated into the model leads to change in PFC and HC volumes. To be clinically useful, we need to ascertain what MMSE score increase is possible with a given duration (in days) of tDCS. For this, we extracted data for the time per day and total number of days of stimulation, average starting MMSE score, and MMSE score increase post-stimulation from the priors. For all studies, the MMSE score increase in treatment group is used. All studies were performed using 2mA tDCS stimulation for 20-30 minutes because it is the most common found in literature. This current level applied for 30minutes a day is used for estimations with this model. The output of the model was the predicted MMSE score increase for a given combination of input features.

In determining which kind of model would best fit the data, polynomial and linear regression models were considered. Since the dataset has a high concentration of data points with 10 or fewer days of stimulation; a polynomial regression model fits very closely to these datapoints, increasing the risk of overfitting. Furthermore, the existence of two long-term tDCS studies would provide undue influence on the line of best fit under a polynomial model. These issues would not be as extreme for a linear regression model. As such, a linear model was chosen to best fit this dataset, where the line of best fit corresponds to

$$\hat{y}=\boldsymbol{\beta x}^{T}=\beta_0+\beta_1 x_1+\beta_2 x_2+\beta_3 x_3 \qquad (5)$$

where ŷ is the predicted MMSE score increase, the

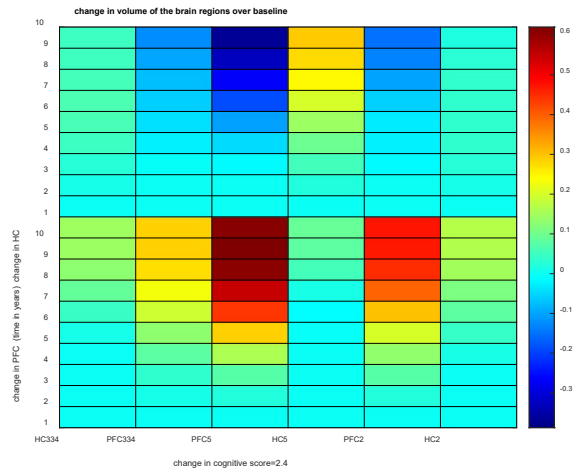

Fig. 4 Mean PFC and HC volumes when alternating PFC and HC stimulation over time. Standard deviations are represented as error bars. Differences are with respect to baseline results at the same year for untreated patients.

vector $\boldsymbol{\beta}$ = [β0 β1 β2 β3] is a vector of weights for the input parameters, β0 is the intercept, and the vector **x** = [x1 x2 x3] is the input vector specifying the time of stimulation per day, number of days of stimulation, and starting MMSE score of the patient respectively. Model was analyzed using the SAS® OnDemand for Academics software using SAS Studio® version 3.81 [23]. The parameters from the model are shown in Table 1. The final linear regression model is statistically significant ($p<0.05$). The model describes roughly 75.22% of variation in the data set. An analysis of Cook's distance for the model reveals no points have undue influence over the model's fit, as none are above a 0.5 threshold. Residuals appear to be normally distributed, indicating equal variances within the data. Furthermore, the quantile vs. residual plot indicates that the error has no bearing on the specific values of the input parameters.

Table 1 Weights for the MMSE Linear Regression Model

Input Feature (xi)	Weight (βi)
Time Per Day (x1)	-0.17392 (β1)
Number of Days (x2)	0.06499 (β2)
Starting MMSE Score (x3)	-0.213572 (β3)
Intercept	9.18036 (β_o)

These coefficients were used to estimate the number of days of stimulation required for 30 minutes a day for different initial MMSE scores to achieve an increase of either 6 or 9 on the MMSE score values. The MMSE score increase of either 6 or 9 points above the baseline was chosen because the increase in brain volume saturates after this for single region stimulation (which was observed to be the best possible stimulation modality). Pre-stimulation MMSE score and the associated number of days to achieve the score increases of 6 or 9 points are shown

in Table 2. The number of days to achieve the required improvement in brain volume can guide the clinicians to help the AD patients.

Table 2 Number of days of active anodal tDCS stimulation needed to achieve an MMSE score increase of 6 or 9 points when stimulation is performed at 2 mA for 30 minutes a day.

Starting MMSE Score	Days to Achieve an MMSE Score Increase of 6	Days to Achieve an MMSE Score Increase of 9
10	64	279
11	67	290
12	70	300
13	73	310
14	76	320
15	80	330
16	83	340
17	86	350
18	89	361
19	92	371
20	96	381
21	99	391
22	102	N/A (MMSE cannot exceed 30)
23	105	N/A
24	108	N/A

5. Discussion and Conclusion

The inclusion of a stimulation parameter in the ADPM models the effect of tDCS on AD patients. The model determines how different cognitive score increases per year can affect brain region volumes over a decade. Based on the results, the single region stimulation is the most effective at increasing volume of the corresponding region among all the stimulation protocols (dual region for 10 years or interleaved stimulation of HC and PFC). Alternating stimulation can produce comparable results in the case of PFC volumes when compared to single region stimulation, but at the expense of decreasing HC volumes.

Given that higher brain volumes are linked to increased brain activity and better cognitive health [21], single region stimulation seems to be better over alternatives when applying tDCS device. Determining which region to stimulate can be done by analyzing the disease quantum from MRI of the brain. If the quantum of disease is more in the HC, then HC should be stimulated and if the disease is more in PFC, then PFC should be stimulated. A stimulation level corresponding to an MMSE increase of 6 or 9 seems to be enough as beyond this point, the gain in brain volume saturates. To individualize the treatment, each patient's initial MMSE score can decide the number of days required with 30 minutes of stimulation applied everyday (Table 2).

To conclude, this work examines the impact of tDCS stimulation on AD patients. It utilizes an existing model to simulate AD progression with tDCS over ten years by modifying the model based on priors. Further, it creates a model to link the level of current stimulation to brain health improvement and suggests a recommended level of tDCS stimulation.

6. Limitations and Future Work

Future iterations of the ADPM may be required to effectively encapsulate various aspects of the disease. This work proposes extension of the model that can evaluate the effects of intervention in disease progression, but other forms of treatment would have to be modeled differently. Furthermore, in its current state, the model does not have many parameters to adjust as many of the parameters are linked together, changing one leads to numerous undesirable effects. This makes updating the model tedious, as introducing a new parameter, or updating an existing parameter can alter calculations for other parameters beyond the initial scope of the modification. Another limitation of this model is that it is very tightly bound by parameters and does not capture variation in patient data. Hence, results for all patients move in same direction as the effect of treatment is added to perturb the model. The results from this work can guide future research in the field or even treatment of patients with the disease.

7. References

[1] Centers for Disease Control and Prevention, "Alzheimer's Disease and Related Dementias," *CDC*, Oct. 26, 2020. https://www.cdc.gov/aging/aginginfo/alzheimers.htm

[2] K. V. Saboo, A. Choudhary, Y. Cao, G. A. Worrell, D. T. Jones, and R. K. Iyer, "Reinforcement Learning based Disease Progression Model for Alzheimer's Disease," *arXiv (Cornell University)*, Jun. 2021, doi: https://doi.org/10.48550/arxiv.2106.16187.

[3] L. Kurlowicz and M. Wallace, "The Mini-Mental State Examination (MMSE)," *Journal of Gerontological Nursing*, vol. 25, no. 5, pp. 8–9, May 1999, doi: https://doi.org/10.3928/0098-9134-19990501-08.

[4] H. Thair, A. L. Holloway, R. Newport, and A. D. Smith, "Transcranial Direct Current Stimulation (tDCS): a Beginner's Guide for Design and Implementation," *Frontiers in Neuroscience*, vol. 11, no. 1, Nov. 2017, doi: https://doi.org/10.3389/fnins.2017.00641.

[5] V. Saxena and A. Pal, "Role of Transcranial Direct Current Stimulation in the Management of Alzheimer's Disease: A Meta-analysis of Effects, Adherence and Adverse Effects," *Clinical Psychopharmacology and Neuroscience*, vol. 19, no. 4, pp. 589–599, Nov. 2021, doi: https://doi.org/10.9758/cpn.2021.19.4.589.

[6] N. News, "Brain Stimulation Enhances Alzheimer's Cognitive Function," *Neuroscience News*, Dec. 06, 2023. https://neurosciencenews.com/tdcs-alzheimers-cognition-25325/

[7] E. M. Khedr, R. H. Salama, M. A. Hameed, N. A. El-Fetoh, and P. Seif, "Therapeutic Role of Transcranial Direct Current Stimulation in Alzheimer Disease Patients: Double-Blind, Placebo-Controlled Clinical Trial," *Neurorehabilitation and Neural Repair*, vol. 33, no. 5, pp. 384–394, Apr. 2019, doi: https://doi.org/10.1177/1545968319840285.

[8] E. M. Khedr *et al.*, "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*, vol. 6, Oct. 2014, doi: https://doi.org/10.3389/fnagi.2014.00275.

[9] A. Gangemi, B. Colombo, and R. A. Fabio, "Effects of short- and long-term neurostimulation (tDCS) on Alzheimer's disease patients: two randomized studies," *Aging Clinical and Experimental Research*, vol. 33, no. 2, pp. 383–390, Apr. 2020, doi: https://doi.org/10.1007/s40520-020-01546-8.

[10] M. Cotelli *et al.*, "Anodal tDCS during face-name associations memory training in Alzheimer's patients," *Frontiers in Aging Neuroscience*, vol. 6, Mar. 2014, doi: https://doi.org/10.3389/fnagi.2014.00038.

[11] O. K. Grønli, I. Daae Rasmussen, P. M. Aslaksen, and M. Bystad, "A four-month home-based tDCS study on patients with Alzheimer's disease," *Neurocase*, vol. 28, no. 3, pp. 276–282, May 2022, doi: https://doi.org/10.1080/13554794.2022.2100710.

[12] Jooyeon Jamie Im *et al.*, "Effects of 6-month at-home transcranial direct current stimulation on cognition and cerebral glucose metabolism in Alzheimer's disease," *Brain Stimulation*, vol. 12, no. 5, pp. 1222–1228, Sep. 2019, doi: https://doi.org/10.1016/j.brs.2019.06.003.

[13] P. S. Boggio et al., "Prolonged visual memory enhancement after direct current stimulation in Alzheimer's disease," Brain Stimulation, vol. 5, no. 3, pp. 223–230, Jul. 2012, doi: https://doi.org/10.1016/j.brs.2011.06.006.

[14] M. Bystad et al., "Transcranial direct current stimulation as a memory enhancer in patients with Alzheimer's disease: a randomized, placebo-controlled trial," Alzheimer's Research & Therapy, vol. 8, no. 1, Mar. 2016, doi: https://doi.org/10.1186/s13195-016-0180-3.

[15] M. A. Gomes, H. T. Akiba, J. S. Gomes, A. P. Trevizol, A. L. T. de Lacerda, and Á. M. Dias, "Transcranial direct current stimulation (tDCS) in elderly with mild cognitive impairment: A pilot study," Dementia & Neuropsychologia, vol. 13, no. 2, pp. 187–195, Jun. 2019, doi: https://doi.org/10.1590/1980-57642018dn13-020007.

[16] C.-S. Chu et al., "Cognitive effects and acceptability of non-invasive brain stimulation on Alzheimer's disease and mild cognitive impairment: a component network meta-analysis," Journal of Neurology, Neurosurgery & Psychiatry, vol. 92, no.2, pp. 195–203, Oct. 2020, doi: https://doi.org/10.1136/jnnp-2020-323870.

[17] H. Lu, S. S. M. Chan, W. C. Chan, C. Lin, C. P. W. Cheng, and L. Linda Chiu Wa, "Randomized controlled trial of TDCS on cognition in 201 seniors with mild neurocognitive disorder," Annals of Clinical and Translational Neurology, vol. 6, no. 10, pp. 1938–1948, Sep. 2019, doi: https://doi.org/10.1002/acn3.50823.

[18] E. Fileccia et al., "Effects on cognition of 20-day anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex in patients affected by mild cognitive impairment: a case-control study," Neurological Sciences, vol. 40, no. 9, pp. 1865–1872, May 2019, doi: https://doi.org/10.1007/s10072-019-03903-6.

[19] Hu et al., "Efficacy and safety of simultaneous rTMS-tDCS over bilateral angular gyrus on neuropsychiatric symptoms in patients with moderate Alzheimer's disease: A prospective, randomized, sham-controlled pilot study," Brain Stimulation, vol. 15, no. 6, pp. 1530–1537, 2022, doi: https://doi.org/10.1016/j.brs.2022.11.009.

[20] Takuma Inagawa, Y. Yokoi, Z. Narita, Kazushi Maruo, M. Okazaki, and Kazuyuki Nakagome, "Safety and Feasibility of Transcranial Direct Current Stimulation for Cognitive Rehabilitation in Patients With Mild or Major Neurocognitive Disorders: A Randomized Sham-Controlled Pilot Study," Frontiers in Human Neuroscience, vol. 13, Sep. 2019, doi: https://doi.org/10.3389/fnhum.2019.00273.

[21] Z. Qing and G. Gong, "Size matters to function: Brain volume correlates with intrinsic brain activity across healthy individuals," *NeuroImage*, vol. 139, pp. 271–278, Oct. 2016, doi: https://doi.org/10.1016/j.neuroimage.2016.06.046

[22] M. W. Weiner *et al.*, "Impact of the Alzheimer's Disease Neuroimaging Initiative, 2004 to 2014," *Alzheimer's & Dementia*, vol. 11, no. 7, pp. 865–884, Jul. 2015, doi: https://doi.org/10.1016/j.jalz.2015.04.005.

SAS® OnDemand for Academics (3.81). SAS Institute. Accessed: Apr. 9, 2024. [Online]. Available: https://welcome.oda.sas.com/