Transcranial Direct Current Stimulation in Alzheimer's Disease: Long-term impact

Anu Aggarwal, member IEEE
Department of Electrical Engineering
California Polytechnic State University, San Luis Obispo CA USA

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. tDCS is a new emerging treatment modality for AD. The impact of tDCS has so far been only sparsely studied in AD patients over a short duration in small sample sizes. Since AD is a progressive disease, it is useful to know about the impact of tDCS over a longer duration and predict the duration and site of treatment. This paper integrates limited data from tDCS treatment of AD patients and extrapolates it to a decade using the AD prediction model (ADPM). Based on this, it provides guidelines for best site and duration of treatment for a patient with AD.

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 and adversely impacts the activities of daily living [115]. 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.

According to [28], [35]-[37], AD is characterized by accumulation of extracellular beta-amyloid plaques and neuronal p-tau [45], [46] in the brain. E4 allele of the apoE gene is highly enriched in neurodegeneration associated neuroglia [38]-[40], and increases the protein kinases responsible for tau phosphorylation [41]-[44]. As the disease advances, there is reduction in brain volume [106]-[113] due to fibrosis after the abnormal protein deposits trigger inflammation. Even though decline in brain volume is observed in healthy controls with ageing (0.5% per year), it is significantly faster in patients with AD (1-3% per year) and the severity depends on whether the AD is familial (early onset, faster decline) or sporadic. Thus, measuring brain volume on MRI is one of the ways to determine disease progression in AD.

Disease diagnosis and progression are indicated by changes in brain size on MRI [52][53], fMRI [54][55] can detect change in neuronal activity, PET [56]-[59] can detect amyloid and p-tau deposits, and clinical examination (MMSE) can detect cognitive changes [49]-[51] as the disease progresses [35]. These can be used to monitor disease progression among other things like CSF or plasma levels of amyloid beta 42/40 ratio, p-tau, neurofilament light chains, and glial fibrillary acidic protein [60]-[71]. The disease is also associated with increased metabolic injury and metabolic markers like cytokines, interleukins etc. [47][48]. The metabolic markers have often been used to target various treatments [29]-[35] in the disease like block receptors for interleukins and cytokines. Other treatment modalities include gene editing to increase TRIM11 and p-tau clearance, decrease APOE and TREM-2 to reduce beta amyloid formation among others. More recent treatment modalities include deep brain stimulation, trans-cranial direct current stimulation (tDCS), cognitive stimulation, rehabilitation, physical exercise and lifestyle modification [72]-[106].

However, documented use of tDCS 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 groups 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 short-term tDCS studies to a period of a decade using the Alzheimer's Disease Progression Model (ADPM) [2].

2. Background

The ADPM uses data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) [22] for 100 patients. This data contains PET images of patient brains to detect the amyloid pathology, MRI images to determine size of the hippocampus and pre-frontal cortex, and MMSE score detected on clinical examination. The above data for all the patients is available over a 10-year follow-up period. fMRI data to estimate brain activity is not available from the ADNI dataset. The ADPM uses differential equations based on brain physiology and pathology to model disease progression and cognitive scores over a 10-year period. Since information on brain activity is not available from the fMRI, the ADPM tries to estimate it using reinforcement learning.

According to the model, baseline amyloid accumulation can be studied using PET. Over a period, the amyloid propagates to other areas of the brain along the white matter tracts. Amyloid accumulation affects the brain region size – increasing it initially and then reducing it. Brain structure can predict brain activity which in turn results in cognition. Conversely, brain activity also depends on cognitive task difficulty. Additionally, brain activity has a metabolic cost which

can enhance degeneration. To represent this mathematically, the model 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. Further, $D_v(t)$ is the instantaneous amyloid accumulation in the brain region v at time t determined using PET images. Incremental amyloid deposition depends on initial amyloid deposition using the following equation

$$\frac{dD(t)}{dt} = -\beta H D(t) \quad (1)$$

Where β is a constant and H is a hessian matrix linking amyloid progression to the two brain regions. 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:

$$Y_v(t) = \gamma \frac{I_v(t)}{X_v(t)} \; \forall v \in V \quad (2)$$

where γ is a constant. This relationship is so defined because as brain activity increases, information processed by a region increases, hence a direct relationship between the two. As the disease progresses, leading to decrease in size of the brain region, its efficiency will be reduced. This will require more activity for the same amount of information processing. Information processed by each region adds up to form the total cognitive demand on the brain. The ADPM estimates the cognitive score, $C(t)$ by summing $I_v(t)$ across the two brain regions.

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

$I_v(t)$ can be obtained from fMRI data but this is not part of the ADNI dataset. Thus, reinforcement learning was used to decipher $I_v(t)$. Furthermore, the ADPM relates brain region volume with amyloid deposition and brain activity as:

$$\frac{dX_v(t)}{dt} = -\alpha_1 D_v(t) - \alpha_2 Y_v(t) \quad (4)$$

where α_1 and α_2 are constants. This equation relates the disease pathology, brain activity and change in brain size. Amyloid reduces the size of brain and brain activity supporting cognition can further accelerate degeneration. Hence, it can reduce the size of the brain by depositing amyloid. The linear relationship comes from prior studies [27]. The model parameters (α_1, α_2, β, γ) were calculated from the demographic features of the population in ADNI.

As mentioned earlier, reinforcement learning (RL) was used to learn the $I_v(t)$ by solving an optimization problem based on two competing criteria, viz., minimizing the difference between cognitive demand of a task (C_{task}) and $C(t)$ provided by the two regions and minimizing the energy costs, $M(t)$ for supporting the cognition. The $M(t)$ is defined as the sum of all the activities of different regions by the following equation.

$$M(t) = \sum_{v \in V} Y_v(t) \quad (5)$$

In the RL, the state consists of the current size of the brain regions, $X(t)$ and the information processed by each region at a prior time point $I(t-1)$. Action is the change in information processed at each time point, $\Delta I(t)$. The environment is a simulator consisting of all the above equations. Based on the action, the environment updates the state and provides a reward to the RL agent. The goal of the policy agent is to maximize the following reward.

$$R(t) = -[\lambda\big(C_{task} - C(t)\big) + M(t)] \quad (6)$$

The RL agent was trained on the simulator with model free on-policy learning using TRPO for 1 million epochs of batch size 1000. There were 32 hidden units in each of the two-layer feedforward network. It was implemented using Open AI's Gym framework. λ and $Io(t)$ were chosen using grid search to choose a value that minimized the validation set error.

$C(t)$ was set to the MMSE score normalized to lie between 0-10. C_{task} is the maximum cognition across the regions and was fixed at 10. The brain region volume taken from the MRI data from ADNI was normalized to lie between 3.5-5.5. This model successfully modelled the Alzheimer's disease progression over a 10 year period with lower MSE[1] than previous models like the miniRNN [24] and support vector regression [25]. It also performed better than models without RL like [26]. While the ADPM models disease progression over a period, it does not study the impact of tDCS which the current work studies.

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 tDCS treatment involves running a weak constant (direct current or DC) electrical current (~2mA) through anodal target electrodes placed on a patient's scalp (like EEG electrodes). The electrodes can be placed

[1] Mean squared error

such that a specific brain area can be stimulated [4]. Treatment duration in each session and number of sessions varies in the clinical studies [7-20] as summarized below and Table 1.

In [7], there were treatment and matched sham groups with 23 subjects each. All had probable AD diagnosis. Subjects in the treatment group received 10 sessions of anodal tDCS 2 mA over the left and right temporoparietal region for 20 minutes for each side with the cathode on the left arm, 5 sessions per week for 2 consecutive weeks. All subjects were assessed using the Modified Mini Mental State Examination (MMMSE) and other related indicators before and after the 10th session. There was a significant improvement in the total score of MMMSE in the treatment group, whereas no such change was observed in the sham group.

In [8], 34 AD patients were randomly assigned to three groups: anodal (11), cathodal (12), and sham (11) tDCS. Stimulation was applied over the left dorsolateral prefrontal cortex for 25 min at 2 mA daily for 10 days. Each patient was submitted to the MMSE and other tests at base line, after the 10th session and at 1 and 2 months after the end of the sessions. *Post hoc* comparisons showed that both anodal and cathodal tDCS (ctDCS) improved MMSE in contrast to sham tDCS that showed decline in MMSE scores. Increase in MMSE scores continued the trend even after a month of treatment but started plateauing after 2months.

In [9], the authors studied short and long-term impact of tDCS on two groups of patients with advanced AD. Anodal tDCS 2mA for 20minutes a day was given to 26 patients for 10 days and to 18 patients for 10 days a month for 8months. Each was compared against matched sham group. MMSE of the groups was recorded pre- and post-test. While the test group's MMSE scores dropped a little over the observation period, that of the sham group dropped significantly lower.

In [10], 12 AD patients were assigned to each of the 3 study groups – analog tDCS plus individualized computerized memory training; placebo tDCS plus individualized computerized memory training; analog tDCS plus motor training. All treatment groups received 5days a week of 2mA of tDCS stimulation over the left DLPFC for 25mins a day for 2 weeks. The reference electrode was placed on the right deltoid muscle. MMSE scores were recorded before, immediately after, 1month and 2months after treatment. The results failed to show significant effect of tDCS alone on MMSE scores.

In [11], 2mA of anodal tDCS was applied for 30minutes daily for 4months in 8 patients with mild AD using home-based equipment. Surface based electrodes with saline soaked sponges were used. Anode was placed over left temporal lobe and cathode over right dorsolateral prefrontal cortex (corresponding to T7 & F4 EEG electrodes respectively). The patients were evaluated using before and after cognitive score assessment at beginning of the study, end of the study and 4months after the end. There was a mean increase in cognitive score observed from baseline at 4months, and a slight decrease at 8months from baseline. In this study, control is not applied for effect of disease progression on cognitive scores.

In [12], patients with early AD were randomized to active (n = 11) or sham tDCS (n = 7) over the dorsolateral prefrontal cortex (DLPFC) at home every day for 6 months (anode F3/cathode F4, 2 mA for 30 minutes). All patients underwent neuropsychological tests and other tests at baseline and 6-month follow-up. Compared to sham tDCS, active tDCS improved global cognition measured with MMSE among other things.

In [13], 15 patients were provided with tDCS bilaterally through two scalp anodal electrodes placed over the temporal regions and a reference electrode over the right deltoid muscle. The stimulating current was set at 2 mA intensity and was delivered for 30 minutes per day for 5 consecutive days. All participants acted as their own control. Treatment and sham were provided at an interval of 71-77 days. Cognitive functions were evaluated before, immediately after, 1 week and 4 weeks after tDCS. In active treatment group the visual recognition memory improved by 8.99% from baseline and the improvement persisted for at least 4 weeks after therapy, whereas for sham group it decreased by 2.62%.

In [14], 12 patients with AD received tDCS in six 30-minute sessions over 10 days. tDCS was delivered to the left temporal cortex with 2-mA intensity - the anode was placed at the T3 position and the cathode was placed on the right frontal lobe at the Fp2 position. They were evaluated using MMSE amongst other tests before and after treatment against 13 matched shams. There were non-significant differences in score changes on the MMSE, among other tests.

In [15], a current of 2.0 mA was applied for 30 minutes for 10 sessions, twice a week to 29 patients of AD in the treatment group. The anode was placed over the left dorsolateral prefrontal cortex (DLPFC). Subjects were evaluated before, immediately and 90 days after the intervention by the MMSE and other tests against 29 patients in the sham group. After 10 sessions of tDCS, no significant differences were observed between the tDCS and Sham groups for MMSE but improvement was seen on other indicators of the disease.

In [16], a network meta-analysis of 27 randomized

controlled trials of anodal tDCS and other brain stimulation studies was conducted. They observed that a-tDCS improved the MMSE score of patients with AD by 0.56 in the short-term (<1month) and by 0.21 over longer term (>1month) in patients with AD but not with MCI.

In [17], 201 patients with mild AD were randomly assigned to 3 groups for a 4-week intervention of either a combination of tDCS and working memory training (WMT), sham tDCS and WMT, or tDCS and control cognitive training (CCT). The anodal electrode was positioned over left lateral temporal cortex (i.e., T3 in the international 10/20 EEG system) and the cathodal over the contralateral upper limb. The stimulation was applied for 20 min at 2 milliamps, with three 45min sessions per week, for 4 weeks. Global cognition and domain-specific cognitive function were assessed at baseline, 4th week, 8th week and 12th week with Cantonese MMSE among other tests. Cognitive enhancement was found across three groups after 4 weeks of intervention.

In [18], 34 patients with mild AD were randomly assigned to the anodal tDCS or sham group. The tDCS group received 2-mA anodal stimulation over the left DLPFC for 20 min, 5 days per week (up to a total of 20 days). MMSE scores among other neuropsychological assessments were done before and post-stimulation. Patients in the treatment showed improvement in MMSE scores among other things.

In [19], 84 AD patients were randomized to receive rTMS-tDCS, single-rTMS, single-tDCS, or sham stimulation on bilateral angular gyrus (AG) for 4 weeks, with evaluation at week-4 and week-12 using MMSE and other cognitive tests. The anode was applied to the AG (P5/P6, 10-10 International EEG System), and the cathode was applied to the contralateral prefrontal area (Fp2/Fp1). After stimulation of the left AG for 15 min, the anode was moved to the right AG, and the cathode was switched from Fp2 to Fp1 for another 15 min. In tDCS treatment group there was improvement in MMSE scores at the end of treatment with slight drop at 12 weeks after treatment period. In the sham group, there was a fall in MMSE scores.

In [20], patients with mild or major neurocognitive disorders were recruited. The participants in the active arm received tDCS on DLPFC (anodal F3, cathodal Fp2, 2mA, 20 min) twice daily for 5 consecutive days, whereas those in the sham arm received the same amount of sham-tDCS. Calculation and reading tasks were conducted in both arms as a form of cognitive intervention for 20 min during tDCS. The primary outcome was the attrition rate during the trial in the active arm, which is expected to be less than 10%. The secondary outcomes were the between-group differences of adjusted means for several cognitive scales from baseline to post-intervention and follow-up. 20 patients participated; 9 with minor neurocognitive disorders and 11 with major neurocognitive disorders were randomized, and 19 of them completed the trial. Patients in the active arm showed no statistically significant improvement compared with those who received the sham in the mean change scores of the MMSE at day five.

Table 1 Change in MMSE scores in prior studies using tDCS [7]-[20].

Study	Change in MMSE scores	
	Active tDCS	**Sham**
Khedr et. al. 2019	+3.5	-0.6
Khedr et. al. 2014	+1.6, +4, +4 immediately, 1month and 2month after	1.5, -0.5, -1 immediately1month and 2month after
Gangemi et. al.	-0.3	-2.3
Cotelli et. al.	0.5, -0.4, -0.5 after 2 weeks of treatment, at 3months and 6months after (tDCS + cognitive training)	0.9, -0.3, 0.2 after 2 weeks of treatment, at 3months and 6months after
Gronli et. al.	+1, -1 after 4months and 8months of study start	NA
Im et. al	+1.1	-1.5
Boggio et. al.	+0.1, 0.9, -0.1 at 0, 1, 4weeks after treatment	+0.3, 0.7, 0.2 at 0, 1, 4weeks after treatment
Bystad, et. al.	+1	+1
Gomes et. al.	+0.3	No change
Chu et. al.	+0.56, +0.21	NA
Lu et. al.	+1, 0.7, 0.5	+0.7, 0.5, 0.5 (with WMT intervention)
Fileccia et. al.	+0.7	-0.5
Hu et. al.	+3.3, -2.9 post treatment and 12 weeks after	+0.2, -1.1 post treatment and 12 weeks after
Inagawa et. al.	0.41, 1.08 more than sham cases immediately and 2 weeks after treatment	NA

There are several ways in which tDCS could modify disease progression in Alzheimer's. The tDCS has been demonstrated to have local impacts on the GABA/glutamate balance - anodal tDCS decreasing and cathodal increasing the GABA-ergic inhibition

[116], to influence functional connectivity, synchronization, and oscillatory activities in prefrontal cortex in healthy individuals as determined by EEG and low resolution tomography [119], tDCS may cause glial stimulation [118] which leads to neurotransmitter release, or could potentially modulate the conformation of beta-amyloid proteins [117] involved in the progression of AD. tDCS has also been shown to increase LTP-like plasticity [114] in human cerebral cortex.

All of the above summarizes how the ADPM provides AD projection over a decade as supported by ADNI data set, the design and results of the limited clinical studies on tDCS and the studies on mechanism of action of tDCS indicate clear benefit of tDCS in AD. Thus, to understand the long-term impact, the area and duration for which tDCS should be applied in a patient with AD, we modified the ADPM in the current work, to incorporate the impact of tDCS stimulation of either the HC, the PFC or both over a period of a decade.

3. Methods

The ADPM was modified to integrate the impact of tDCS on cognitive scores, as estimated from prior studies [7-20].

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:

$$\hat{I_v}(t) = I_v(t) - \Delta I_{stim} \qquad (7)$$

$\hat{I_v}(t)$ replaces all instances of $I_v(t)$ in equations (2) 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 (4). 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).

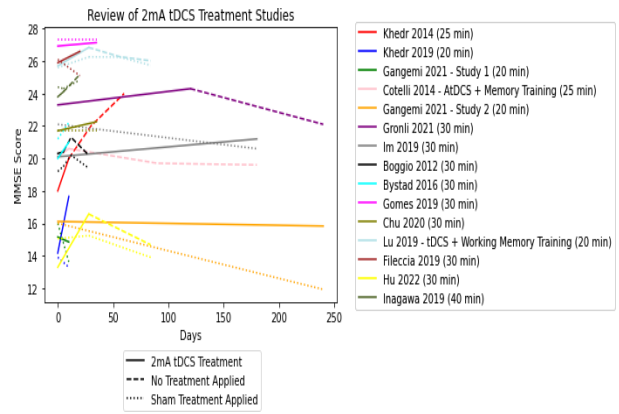

Fig. 1 The effect of tDCS stimulation on cognitive scores in Alzheimer's patients from priors [7-20]. The graph on the left shows the change in cognitive score for stimulation with 2mA tDCS over the number of days shown. Right column references the study from which the data is taken along with the time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

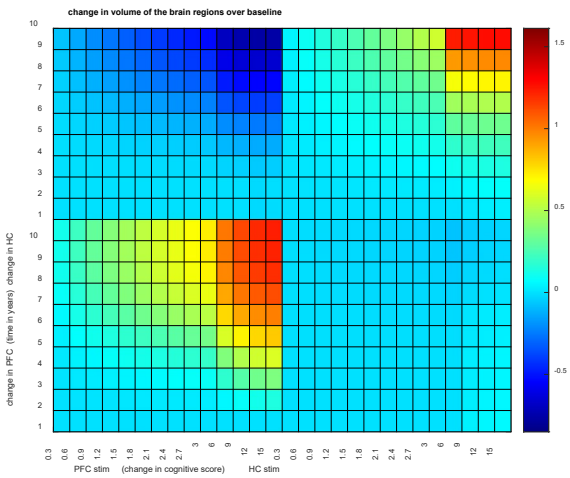

Fig. 2 Showing mean change in HC and PFC volume over a period of 10 years when different current stimulation and corresponding change in MMSE scores was applied over a period of 10years in the ADPM. Change in volume is with respect to baseline results for the same year when patient did not receive any 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.

The largest changes in PFC or HC volume occur when stimulating only the respective region. Across all 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. And 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).

4.2 Simultaneous PFC and HC Stimulation

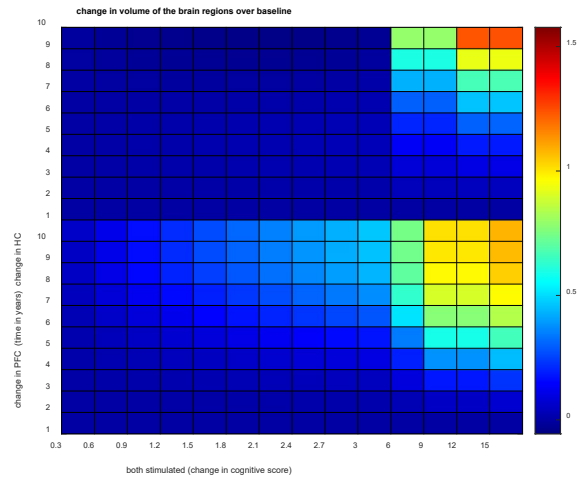

Fig. 3 Mean change in PFC and HC volume over a period of 10 years when different current stimulation and corresponding change in MMSE scores was applied in the ADPM – with half the stimulation applied to HC and the other half to the PFC. Differences are with respect to baseline results at the same year 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.

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 like 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.

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.

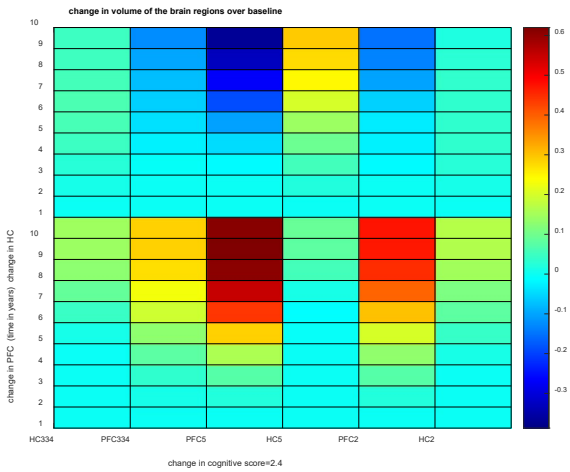

Fig. 4 Mean PFC and HC volumes when alternating PFC and HC stimulation over time. Standard deviations are represented as error bars. Differences are with respect to baseline results at the same year for untreated patients.

From Fig. 4, it is evident that the maximum change in non-normalized PFC volume at year 10 was 16755 mm^3, which is like 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 10,826 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

From the results in sections above, we identified the region of the brain which needs stimulation in a patient with AD. To be clinically useful, we also need to ascertain the duration of tDCS treatment (in days) for a level of MMSE score increase in the patient. 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 20-40 minutes because it is the most common found in literature. We fixed two of the parameters – 2mA current level applied for 30minutes a day to estimate the number of days required for improvement in cognitive scores based on MMSE. 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 a concern 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 $\hat{y}$ is the predicted MMSE score increase, the vector $\boldsymbol{\beta} = [\beta 0\ \beta 1\ \beta 2\ \beta 3]$ is a vector of weights for the input parameters, $\beta 0$ is the intercept, and the vector $\mathbf{x} = [x1\ x2\ x3]$ is the input vector specifying the time of stimulation per day, number of days of stimulation, and starting MMSE score of the patient respectively. The parameters from the model are shown in Table 2.

Table 2 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_0)

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 score increases of 6 or 9 points are shown in Table 3. The number of days to achieve the required

improvement in brain volume can guide the clinicians to help the AD patients.

Table 3 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 increase 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. 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 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 3). In determining this, we also need to be aware that the patient's cognitive score will change over a period due to the underlying disease. Hence, the treatment required might have to be continuous and not just one time.

Model was analyzed using the SAS® OnDemand for Academics software using SAS Studio® version 3.81 [23]. 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 (Fig. 5). 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.

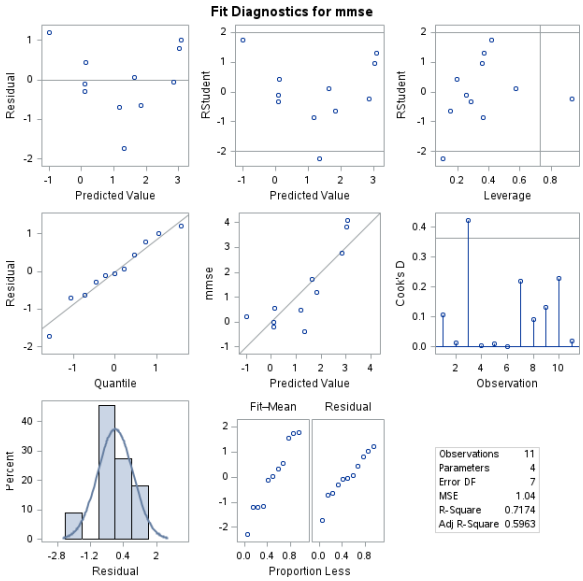

Fig 5. Fit and Residual Statistics for the MMSE Linear Regression Model

To conclude, this work examines the impact of tDCS stimulation on brain volume and quantum of disease in 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 MMSE score improvement and suggests a duration 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.

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.

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

[24] M. Nguyen, T. He, et. al., 2020, "Predicting alzheimers disease progression using deep recurrent neural networks", *NeuroImage,* 222:117203.

[25] L.L. Raket, 2020, "Alzheimers Disease Neuroimaging Initiative, et. al. Statistical modeling in Alzheimers disease", *Frontiers in Big Data,* 3, 2020.

[26] A. Raj, A. Kuceyeski, M. Weiner, et. al. 2015, "A network diffusion model of progression predicts longitudinal patterns of atrophy and metabolism in alzheimer's disease", *Cell reports*, 10(3):359-369.

[27] F. G. Hillary, J.H. Grafman, 2017. "Injured brains and adaptive networks: the benefits and costs of hyperconnectivity", *Trends in cognitive neurosciences,* 21(5):385-401.

[28] EJ Goetzel, 2025, "Current developments in Alzheimer's Disease", *American Journal of Medicine,* 138:15-20.

[29] Goetzl EJ, Abner EL, Jicha GA, Kapogiannis D, Schwartz JB, "Declining levels of functionally specialized synaptic proteins in plasma neuronal exosomes with progression of Alzheimer's disease. *FASEBJ*, 2018; 32(2):888–93.

[30] Zhang ZY, Harischandra DS, Wang R, etal. "TRIM11 protects against tauopathies and is down-regulated in Alzheimer's disease", *Science*, 2023; 381(6656):eadd6696.

[31] Qi F, Xu X, Guo X, Luo J, Li Y, Yan S., "Editorial : application of gene editing in neurodegenerative diseases", volumeII. *FrontNeurosci* 2023; 17:1305302.

[32] Li Z, Yin B, Zhang S, Lan Z, Zhang L, "Targeting protein kinases for the treatment of Alzheimer's disease: recent progress and future perspectives", *Eur J Med Chem* 2023; 261:115817.

[33] Ashton NJ, Brum WS, DiMolfetta G, etal, "Diagnostic accuracy of a plasma phosphorylated tau217 immunoassay for Alzheimer disease pathology", *JAMA Neurol* 2024;81(3):255–63.

[34] Li H, Chen Z, Shen Y, etal, "Gene therapy in Ab-induced cell and mouse models of Alzheimer's disease through compensating defective mitochondrial complex I function", *JTranslMed*, 2024; 22(1):760.

[35] P T Kamatham, R Shukla, D K Khatri, L K Vora, 2024, "Pathogenesis, diagnostics and therapeutics for Alzheimer's Disease: Breaking the memory barrier", *Ageing Research Reviews,* 101(2024) 102481. DOI: 10.1016/j.arr.2024.102481.

[36] Murakami, S., Lacayo, P., 2022. Biological and disease hallmarks of Alzheimer's disease defined by Alzheimer's disease genes. Front Aging Neurosci. [Internet] 14, 996030 (Available from: http://alzgene.org/).

[37] Ratan, Y., Rajput, A., Maleysm, S., Pareek, A., Jain, V., Pareek, A., et al., 2023. An Insight into Cellular and Molecular Mechanisms Underlying the Pathogenesis of Neurodegeneration in Alzheimer's Disease. Biomedicines Vol 11, 1398 [Internet]. 2023 May 8 [cited 2024 Jun 28];11(5):1398. Available from: https://www.mdpi. com/2227-9059/11/5/1398/htm.

[38] Kim, J., Basak, J.M., Holtzman, D.M., 2009. The Role of Apolipoprotein E in Alzheimer's Disease. Neuron 63 (3), 287–303.

[39] Liu, C.C., Kanekiyo, T., Xu, H., Bu, G., 2013. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat. Rev. Neurol. 9 (2), 106–118. Available from: https://www.nature.com/articles/nrneurol.2012.263.

[40] Schmechel, D.E., Saunders, A.M., Strittmatter, W.J., Crain, B.J., Hulette, C.M., Joo, S.H., et al., 1993. Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. Proc. Natl. Acad. Sci. USA [Internet] 90 (20), 9649. Available from: /pmc/articles/ PMC47627/?report=abstract.

[41] Hernandez, P., Lee, G., Sjoberg, M., MacCioni, R.B., 2009. Tau phosphorylation by cdk5 and Fyn in response to amyloid peptide Abeta (25-35): involvement of lipid rafts. J. Alzheimers Dis. [Internet] [cited 2024 Jun 25];16(1):149–56. Available from: https://pubmed.ncbi.nlm.nih.gov/19158430/.

[42] Terwel, D., Muyllaert, D., Dewachter, I., Borghgraef, P., Croes, S., Devijver, H., et al., 2008. Amyloid Activates GSK-3β to Aggravate Neuronal Tauopathy in Bigenic Mice. Am. J. Pathol. [Internet] [cited 2024 Jun 25];172(3):786. Available from: /pmc/ articles/PMC2258274/.

[43] Medina, M., Avila, J., 2012. Glycogen Synthase Kinase-3 (GSK-3) Inhibitors for the Treatment of Alzheimers Disease. Curr. Pharm. Des. [Internet] 16 (25), 2790–2798. Available from: https://www.eurekaselect.com/article/17367.

[44] Fu, W., Vukojevic, V., Patel, A., Soudy, R., MacTavish, D., Westaway, D., et al., 2017. Role of microglial amylin receptors in mediating beta amyloid (Aβ)-induced inflammation. J. Neuroinflamm. [Internet] 14 (1), 1–12. Available from: https:// link.springer.com/articles/10.1186/s12974-017-0972-9.

[45] Moloney, C.M., Lowe, V.J., Murray, M.E., 2021. Visualization of neurofibrillary tangle maturity in Alzheimer's disease: A clinicopathologic perspective for biomarker research. Alzheimer'S. Dement. [Internet] 17 (9), 1554–1574. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/alz.12321.

[46] Rajmohan, R., Reddy, P.H., 2017. Amyloid Beta and Phosphorylated Tau Accumulations Cause Abnormalities at Synapses of Alzheimer's disease Neurons. J. Alzheimers Dis. [Internet] [cited 2024 Apr 2];57(4):975. Available from: /pmc/articles/ PMC5793225/.

[47] Kinney, J.W., Bemiller, S.M., Murtishaw, A.S., Leisgang, A.M., Salazar, A.M., Lamb, B.T., 2018. Inflammation as a central mechanism in Alzheimer's disease. Alzheimer'S. Dement.: Transl. Res. Clin. Interv. [Internet] 4 (1), 575–590. Available from: https:// onlinelibrary.wiley.com/doi/full/10.1016/j.trci.2018.06.014.

[48] Wang, W.Y., Tan, M.S., Yu, J.T., Tan, L., 2015. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. Ann. Transl. Med [Internet] 3 (10), 136–136. Available from: https://atm.amegroups.org/article/view/6546/html.

[49] Harvey, P.D., 2019. Domains of cognition and their assessment. Dialog-. Clin. Neurosci. [Internet] [cited 2024 Apr 3];21(3):227–37. Available from: https://www. tandfonline.com/doi/abs/10.31887/DCNS.2019.21.3/pharvey.

[50] Wang, G., Estrella, A., Hakim, O., Milazzo, P., Patel, S., Pintagro, C., et al., 2022. Mini- Mental State Examination and Montreal Cognitive Assessment as Tools for Following Cognitive Changes in Alzheimer's Disease Neuroimaging Initiative Participants. J. Alzheimer'S. Dis. 90 (1), 263–270.

[51] Meyer, J.S., Xu, G., Thornby, J., Chowdhury, M.H., Quach, M., 2002. Is mild cognitive impairment prodromal for vascular dementia like Alzheimer's disease? Stroke [Internet] [cited 2024 Apr 5];33(8):1981–5. Available from: https://pubmed.ncbi. nlm.nih.gov/12154249/.

[52] Vemuri, P., Whitwell, J.L., Kantarci, K., Josephs, K.A., Parisi, J.E., Shiung, M.S., et al., 2008. Antemortem MRI based Structural Abnormality Index (STAND)-Scores Correlate with Postmortem Braak Neurofibrillary Tangle Stage. Neuroimage [Internet]. Aug 8 [cited 2024 Jun 27];42(2):559. Available from: /pmc/articles/ PMC3097053/.

[53] Devanand, D.P., Pradhaban, G., Liu, X., Khandji, A., De Santi, S., Segal, S., et al., 2007. Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease. Neurol. [Internet]. Mar [cited 2024 Jun 26];68(11):828–36. Available from: https://pubmed.ncbi.nlm.nih.gov/17353470/.

[54] Cummings, J., 2019. The Role of Biomarkers in Alzheimer's Disease Drug Development. Adv. Exp. Med Biol. [Internet] [cited 2024 Apr 3];1118:29–61. Available from: https://link.springer.com/chapter/10.1007/978-3-030-05542-4_2.

[55] Maji, S.K., Anoop, A., Singh, P.K., Jacob, R.S., 2010. CSF biomarkers for Alzheimer's disease diagnosis. Int J. Alzheimers Dis.

[56] Klunk, W.E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D.P., et al., 2004. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann. Neurol. [Internet] 55 (3), 306–319. Available from: https://onlinelibrary.wiley. com/doi/full/10.1002/ana.20009.

[57] Xia, C.F., Arteaga, J., Chen, G., Gangadharmath, U., Gomez, L.F., Kasi, D., et al., 2013. [18F]T807, a novel tau positron emission tomography imaging agent for Alzheimer's disease. Alzheimer'S. Dement. [Internet]. Nov 1 [cited 2024 Jun 27];9(6):666–76. Available from: https://onlinelibrary.wiley.com/doi/full/10.1016/j. jalz.2012.11.008.

[58] Cagnin, A., Brooks, D.J., Kennedy, A.M., Gunn, R.N.,

Myers, R., Turkheimer, F.E., et al., 2001. In-vivo measurement of activated microglia in dementia. Lancet [Internet]. Aug 11 [cited 2024 Jun 27];358(9280):461–7. Available from: http://www.thelancet.com/article/S0140673601056252/fulltext.

[59] Zhang, S., Han, D., Tan, X., Feng, J., Guo, Y., Ding, Y., 2012. Diagnostic accuracy of 18F- FDG and 11C-PIB-PET for prediction of short-term conversion to Alzheimer's disease in subjects with mild cognitive impairment. Int J. Clin. Pr. [Internet]. Feb 1 [cited 2024 Jun 27];66(2):185–98. Available from: https://onlinelibrary.wiley.com/doi/ full/10.1111/j.1742-1241.2011.02845.x.

[60] Andersen, E., Casteigne, B., Chapman, W.D., Creed, A., Foster, F., Lapins, A., et al., 2021. Diagnostic biomarkers in Alzheimer's disease. Biomark. Neuropsychiatry 5, 100041.

[61] Hansson, O., Lehmann, S., Otto, M., Zetterberg, H., Lewczuk, P., 2019. Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease. Alzheimers Res Ther. [Internet]. Apr 22 [cited 2024 Apr 3];11 (1):1–15. Available from: https://alzres.biomedcentral.com/articles/10.1186/ s13195-019-0485-0.

[62] Gunes, S., Aizawa, Y., Sugashi, T., Sugimoto, M., Rodrigues, P.P., 2022. Biomarkers for Alzheimer's Disease in the Current State: A Narrative Review. Int. J. Mol. Sci. Vol 23, 4962 [Internet]. 2022 Apr 29 [cited 2024 Apr 5];23(9):4962. Available from: https://www.mdpi.com/1422-0067/23/9/4962/htm.

[63] Klyucherev, T.O., Olszewski, P., Shalimova, A.A., Chubarev, V.N., Tarasov, V.V., Attwood, M.M., et al., 2022. Advances in the development of new biomarkers for Alzheimer's disease. Transl. Neurodegener. 11, 1 [Internet]. 2022 Apr 21 [cited 2024 Apr 5];11(1):1–24. Available from: https://translationalneurodegeneration. biomedcentral.com/articles/10.1186/s40035-022-00296-z.

[64] Wattmo, C., Blennow, K., Hansson, O., 2020. Cerebrospinal fluid biomarker levels: Phosphorylated tau (T) and total tau (N) as markers for rate of progression in Alzheimer's disease. BMC Neurol. [Internet]. Jan 9 [cited 2024 Apr 3];20(1):1–12. Available from: https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-019-1591-0.

[65] Schraen-Maschke S., Sergeant N., Dhaenens C.M., Bombois S., Deramecourt V., Caillet- Boudin M.L., et al. Tau as a biomarker of neurodegenerative diseases. https://doi.org/102217/1752036324363 [Internet]. 2008 Sep 17 [cited 2024 Apr 5];2(4): 363–84. Available from: https://www.futuremedicine.com/doi/10.2217/ 17520363.2.4.363.

[66] Dumurgier, J., Schraen, S., Gabelle, A., Vercruysse, O., Bombois, S., Laplanche, J.L., et al., 2015. Cerebrospinal fluid amyloid-β 42/40 ratio in clinical setting of memory centers: A multicentric study. Alzheimers Res Ther. [Internet] 7 (1), 1–9. Available from: https://alzres.biomedcentral.com/articles/10.1186/s13195-015-0114-5.

[67] McDade, E., Wang, G., Gordon, B.A., Hassenstab, J., Benzinger, T.L.S., Buckles, V., et al., 2018. Longitudinal cognitive and biomarker changes in dominantly inherited Alzheimer disease. Neurology 91 (14), E1295–E1306.

[68] Lle´o, A., Alcolea, D., Martínez-Lage, P., Scheltens, P., Parnetti, L., Poirier, J., et al., 2019. Longitudinal cerebrospinal fluid biomarker trajectories along the Alzheimer's disease continuum in the BIOMARKAPD study. Alzheimers Dement [Internet]. Jun 1 [cited 2024 Apr 5];15(6):742–53. Available from: https://pubmed.ncbi.nlm.nih. gov/30967340/.

[69] Bradburn, S., Murgatroyd, C., Ray, N., 2019. Neuroinflammation in mild cognitive impairment and Alzheimer's disease: A meta-analysis. Ageing Res Rev. [Internet]. Mar 1 [cited 2024 Apr 5];50:1–8. Available from: https://pubmed.ncbi.nlm.nih.gov/ 30610927/.

[70] Hansson, O., Blennow, K., Zetterberg, H., Dage, J., 2023b. Blood biomarkers for Alzheimer's disease in clinical practice and trials. Nat. Aging 3, 5 [Internet]. 2023 May 18 [cited 2024 Apr 5];3(5):506–19. Available from: https://www.nature.com/ articles/s43587-023-00403-3.

[71] Fortea, J., Vilaplana, E., Alcolea, D., Carmona-Iragui, M., S´anchez-Saudinos, M.B., Sala, I., et al., 2014. Cerebrospinal fluid β-amyloid and phospho-tau biomarker interactions affecting brain structure in preclinical Alzheimer disease. Ann. Neurol. [Internet] [cited 2024 Apr 5];76(2):223–30. Available from: https://pubmed.ncbi. nlm.nih.gov/24852682/

[72] Fontaine, D., Santucci, S., 2021. Deep brain stimulation in Alzheimer's disease. Int Rev. Neurobiol. [Internet] [cited 2024 Jun 28];159:69–87. Available from: https:// pubmed.ncbi.nlm.nih.gov/34446251/.

[73] Ríos, A.S., Oxenford, S., Neudorfer, C., Butenko, K., Li, N., Rajamani, N., et al., 2022. Optimal deep brain stimulation sites and networks for stimulation of the fornix in Alzheimer's disease. Nat. Commun. 13, 1 [Internet]. 2022 Dec 14 [cited 2024 Jun 28];13(1):1–14. Available from: https://www.nature.com/articles/s41467-022- 34510-3.

[74] Merrill, C.A., G Jonsson, M.A., Minthon, L., Ejnell, H., C-son Silander, H., Blennow, K., et al., 2006. Vagus Nerve Stimulation in Patients With Alzheimer's Disease: Additional Follow-Up Results of a Pilot Study Through 1 Year. J. Clin. Psychiatry 67 (8).

[75] Vargas-Caballero, M., Warming, H., Walker, R., Holmes, C., Cruickshank, G., Patel, B., 2022. Vagus Nerve Stimulation as a Potential Therapy in Early Alzheimer's Disease: A Review. Front Hum. Neurosci. [Internet]. Apr 29 [cited 2024 Jun 28];16. Available from: /pmc/articles/PMC9098960/.

[76] Yan, L., Li, H., Qian, Y., Zhang, J., Cong, S., Zhang, X., et al., 2024. Transcutaneous vagus nerve stimulation: a new strategy for Alzheimer's disease intervention through the brain-gut-microbiota axis? Front Aging Neurosci. 16, 1334887.

[77] Mahncke, H.W., Bronstone, A., Merzenich, M.M., 2006. Brain plasticity and functional losses in the aged: scientific bases for a novel intervention. Prog. Brain Res 157, 81–109.

[78] Bahar-Fuchs, A., Clare, L., Woods, B., 2013. Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. Cochrane Database Syst. Rev. 6.

[79] McAulay, J., Streater, A., 2020. Delivery of cognitive stimulation therapy for people with dementia in an inpatient setting (innovative practice). Dementia 19 (7), 2513–2520.

[80] Spector, A., Thorgrimsen, L., Woods, B.O.B., Royan, L., Davies, S., Butterworth, M., et al., 2003. Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial. Br. J. Psychiatry 183 (3), 248–254.

[81] Lok, N., Buldukoglu, K., Barcin, E., 2020. Effects of the cognitive stimulation therapy based on Roy's adaptation model on Alzheimer's patients' cognitive functions, coping-adaptation skills, and quality of life: A randomized controlled trial. Perspect. Psychiatr. Care 56 (3), 581–592.

[82] Stinson, C.K., 2009. Structured group reminiscence: an intervention for older adults. J. Contin. Educ. Nurs. 40 (11), 521–528.

[83] Spector, A., Orrell, M., Woods, B., 2010. Cognitive Stimulation Therapy (CST): effects on different areas of cognitive function for people with dementia. Int J. Geriatr. Psychiatry 25 (12), 1253–1258.

[84] Quintana-Hernandez, D.J., Miro-Barrachina, M.T., Ibanez-Fernandez, I.J., Pino, A.S. del, Quintana-Montesdeoca, M.P., Rodriguez-de Vera, B., et al., 2016. Mindfulness in the maintenance of cognitive capacities in Alzheimer's disease: a randomized clinical trial. J. Alzheimer'S. Dis. 50 (1), 217–232.

[85] Camargo, C.H.F., Justus, F.F., Retzlaff, G., 2015. The effectiveness of reality orientation in the treatment of Alzheimer's disease. Am. J. Alzheimers Dis. Other Demen 30 (5), 527–532.

[86] Amieva, H., Robert, P.H., Grandoulier, A.S., Meillon, C., De Rotrou, J., Andrieu, S., et al., 2016. Group and individual cognitive therapies in Alzheimer's disease: the ETNA3 randomized trial. Int Psychogeriatr. 28 (5), 707–717.

[87] Brueggen, K., Kasper, E., Ochmann, S., Pfaff, H., Webel, S., Schneider, W., et al., 2017. Cognitive rehabilitation in Alzheimer's disease: a controlled intervention trial. J. Alzheimer'S. Dis. 57 (4), 1315–1324.

[88] Ruegsegger, G.N., Booth, F.W., 2018. Health Benefits of Exercise. Cold Spring Harb. Perspect. Med 8 (7).

[89] Liu, Y., Tan, Y., Zhang, Z., Yi, M., Zhu, L., Peng, W., 2024. The interaction between ageing and Alzheimer's disease: insights from the hallmarks of ageing. Transl. Neurodegener. 13, 1 [Internet]. 2024 Jan 23 [cited 2024 Mar 26];13(1):1–32. Available from: https://link.springer.com/articles/10.1186/s40035-024-00397-x.

[90] Ross, R.E., VanDerwerker, C.J., Saladin, M.E., Gregory, C.M., 2023. The role of exercise in the treatment of depression: biological underpinnings and clinical outcomes. Mol. Psychiatry 28 (1), 298–328.

[91] Ihira, H., Sawada, N., Inoue, M., Yasuda, N., Yamagishi, K., Charvat, H., et al., 2022. Association Between Physical Activity and Risk of Disabling Dementia in Japan. JAMA Netw. Open 5 (3), e224590.

[92] Pang, R., Wang, X., Pei, F., Zhang, W., Shen, J., Gao, X., et al., 2019. Regular Exercise Enhances Cognitive Function and Intracephalic GLUT Expression in Alzheimer's Disease Model Mice. J. Alzheimers Dis. 72 (1), 83–96.

[93] Liu, Y., Chu, J.M.T., Yan, T., Zhang, Y., Chen, Y., Chang, R.C.C., et al., 2020b. Short-term resistance exercise inhibits neuroinflammation and attenuates neuropathological changes in 3xTg Alzheimer's disease mice. J. Neuroinflamm. 17 (1), 4.

[94] Berchtold, N.C., Prieto, G.A., Phelan, M., Gillen, D.L., Baldi, P., Bennett, D.A., et al., 2019. Hippocampal gene expression patterns linked to late-life physical activity oppose age and AD-related transcriptional decline. Neurobiol. Aging 78, 142–154.

[95] Sanfilippo, C., Musumeci, G., Castrogiovanni, P., Fazio, F., Li Volti, G., Barbagallo, I., et al., 2021. Hippocampal transcriptome deconvolution reveals differences in cell architecture of not demented elderly subjects underwent late-life physical activity. J. Chem. Neuroanat. 113, 101934.

[96] Santiago, J.A., Quinn, J.P., Potashkin, J.A., 2022. Physical Activity Rewires the Human Brain against Neurodegeneration. Int J. Mol. Sci. 23 (11).

[97] Kim, D., Cho, J., Kang, H., 2019. Protective effect of exercise training against the progression of Alzheimer's disease in 3xTg-AD mice. Behav. brain Res. 374, 112105.

[98] Xu, B., He, Y., Liu, L., Ye, G., Chen, L., Wang, Q., et al., 2022. The Effects of Physical Running on Dendritic Spines and Amyloid-beta Pathology in 3xTg-AD Male Mice. Aging Dis. 13 (4), 1293–1310.

[99] Belaya, I., Ivanova, M., Sorvari, A., Ilicic, M., Loppi, S., Koivisto, H., et al., 2020. Astrocyte remodeling in the beneficial effects of long-term voluntary exercise in Alzheimer's disease. J. Neuroinflamm. 17 (1), 271.

[100] Li, Z., Chen, Q., Liu, J., Du, Y., 2020. Physical Exercise Ameliorates the Cognitive Function and Attenuates the Neuroinflammation of Alzheimer's Disease via miR- 129-5p. Dement Geriatr. Cogn. Disord. 49 (2), 163–169.

[101] Gronwald, T., de Bem Alves, A.C., Murillo-Rodríguez, E., Latini, A., Schuette, J., Budde, H., 2019. Standardization of exercise intensity and consideration of a dose- response is essential. Commentary on "Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models", by Lourenco et al., published 2019 in Nature Medic. J. Sport Health Sci. 8 (4), 353–354.

[102] Holth, J.K., Fritschi, S.K., Wang, C., Pedersen, N.P., Cirrito, J.R., Mahan, T.E., et al., 2019. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. Science 363 (6429), 880–884.

[103] Lucey, B.P., Hicks, T.J., McLeland, J.S., Toedebusch, C.D., Boyd, J., Elbert, D.L., et al., 2018. Effect of sleep on overnight cerebrospinal fluid amyloid β kinetics. Ann. Neurol. 83 (1), 197–204.

[104] Sabia, S., Fayosse, A., Dumurgier, J., van Hees, V.T., Paquet, C., Sommerlad, A., et al., 2021. Association of sleep duration in middle and old age with incidence of dementia. Nat. Commun. 12 (1), 2289.

[105] Kivipelto, M., Mangialasche, F., Ngandu, T., 2018. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. In: Nature Reviews Neurology, Vol. 14. Nature Publishing Group, pp. 653–666.

[106] A.F. Fotenos, ScB; A.Z. Snyder, PhD, MD; L.E. Girton, BA; J.C. Morris, MD; and R.L. Buckner, PhD, 2005, "Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD", *Neurology,* 64:1032-1039.

[107] Tang Y, Whitman GT, Lopez I, Baloh RW. Brain volume changes on longitudinal magnetic resonance imaging in normal older people. J Neuroimaging 2001;11:393–400.

[108] Hubbard BM, Anderson JM. A quantitative study of cerebral atrophy in old age and senile dementia. J Neurol Sci 1981;50:135–145.

[109] Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 1997;18:351–357.

[110] Price JL, Ko AI, Wade MJ, Tsou SK, McKeel DW, Morris JC. Neuron number in the entorhinal cortex and CA1 in preclinical Alzheimer disease. Arch Neurol 2001;58:1395–1402.

[111] Jernigan TL, Salmon DP, Butters N, Hesselink JR. Cerebral structure on MRI, part II: specific changes in Alzheimer's and Huntington's diseases. Biol Psychiatry 1991;29:68–81.

[112] Wang DM, Chalk JB, Rose SE, et al. MR image-based measurement of rates of change in volumes of brain structures. Part II: application to a study of Alzheimer's disease and normal aging. Magn Reson Imaging 2002;20:41–48.

[113] Fox NC, Freeborough PA. Brain atrophy progression measured from registered serial MRI: validation and application to Alzheimer's disease. J Magn Reson Imaging 1997;7:1069–1075.

[114] Frase et al. 2021, "Transcranial direct current stimulation induces long-term potentiation-like plasticity in the human visual

cortex", *Translational Psychiatry* 11:17. https://doi.org/10.1038/s41398-020-01134-4.

[115] S. Weintraub, A. H. Wicklund, D.P. Salmon, 2012, "The neuropsychological profile of Alzheimer disease", *Cold Spring Harbor Perspect. Med.* 4:a00617. Doi: 10.1101/cshperspect.a006171.

[116] Stagg, C. J., Best, J. G., Stephenson, M. C., O'Shea, J., Wylezinska, M., Kincses, Z. T., et al. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J. Neurosci. 29, 5202–5206. doi: 10.1523/JNEUROSCI.4432-08.2009.

[117] Toschi, F., Lugli, F., Biscarini, F., and Zerbetto, F. (2009). Effects of electric field stress on a β-amyloid peptide. J. Physic. Chem. B 113, 369–376. doi: 10.1021/jp807896g.

[118] Ruohonen, J., and Karhu, J. (2012). TDCS possibly stimulates glial cells. Clinic. Neurophysiol. 123, 2006–2009. doi: 10.1016/j.clinph.2012.02.082

[119] Keeser, D., Padberg, F., Reisinger, E., Pogarell, O., Kirsch, V., Palm, U., et al. (2011). Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: a standardized low resolution tomography (sLORETA) study. Neuroimage 55, 644–657. doi: 10.1016/j.neuroimage.2010.12.0