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Research Study Title: Understanding how Alzheimer's Disease impacts the therapeutic response to transcranial direct current stimulation

Primary Investigator: Carlos Roncero, Rotman Research Institute, Baycrest Health Sciences, troncero@research.baycrest.org

Co-Investigators: Howard Chertkow, Rotman Research Institute, Baycrest Health Sciences,

hchertkow@research.baycrest.org

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INTRODUCTION:

750,000 Canadians have dementia from Alzheimer Disease or other causes, this number will double within the next generation, and no new therapies have emerged in the past 20 years. However, a new promising therapy is transcranial direct current stimulation (tDCS), a near painless treatment where mild electrical current is applied through the scalp to the brain. This has been found to improve symptoms in people with dementia. Unfortunately, some studies have also reported that tDCS failed to improve symptoms in their participants, so it's important to understand why tDCS seems to work in some cases, but fails to produce an improvement in other cases. One possible reason is the intensity level of tDCS, which is normally 2 mA in studies. Some researchers believe a higher intensity level, 4 mA, would produce a bigger improvement.

LITERATURE REVIEW:

Symptomatic therapy in neurodegenerative diseases (NDD) is very limited. Since introduction of the cholinesterase inhibitors in 1995 and Memantine in 2002, there have been no new available pharmaceutical therapies. As a result, researchers are looking beyond chemicals for a means to ameliorate cognitive impairment. Neuromodulation, particularly tDCS has garnered increasing attention as a potential ancillary symptomatic brain therapy for neurological and psychiatric conditions, reaching the level of being made clinically available for pain and depression [1, 2].

In tDCS, two electrodes (anode and cathode) are secured to the scalp and continuous current flows through the brain from anode to cathode, which modulates corresponding neural activity. It has been theorized that if these neuronal pathways are activated to a certain level, a long-lasting change will occur in the network which allows information to be more easily retrieved or remembered. Consistent with this hypothesis, recent studies at a few centers have shown clinically meaningful improvement in individuals with neurodegenerative diseases treated with transcranial direct current stimulation (tDCS). For instance, we have previously shown a robust effect of improved picture naming [3-4] in individuals with Primary Progressive Aphasia (PPA) and people living with dementia who also suffered from anomia [5]. We have also published case reports where tDCS improved the quality of life in an individual with advanced dementia [6] and walking speed in a person with Progressive Supranuclear Palsy [7]. Others have found similar results [8-10].

Despite these encouraging results, studies examining tDCS for people with dementia have produced variable results. For example, Khedr et al. [11] reported positive tDCS effects, whereas Cottelli et al.[12] and Suemoto et al.[13] reported no improvement or equivalence to a placebo condition. Neuromodulation, however, is both diverse and relatively recent, with differences between approaches, techniques, and electrode montages across studies, making it difficult to compare results. As reported by Prehn and Flöel [14] in their review of tDCS for people with dementia: “The most effective stimulation parameters for enhancing cognitive function in older subjects and patients with AD and MCI are still unclear.”

Our research has increasingly focused on identifying the parameters that increase efficacy. For example, in our previous study [5], we found a montage focused on the parietal lobe was superior to one focused on the dorsolateral prefrontal cortex (DLPFC) for improving naming ability.

Finding such parameter optimizations is critical for advancing tDCS as a therapy for people with dementia as we learn to tailor its administration. In the current project, our central goal is to examine a critical additional stimulation parameter: intensity.

RATIONALE:

tDCS studies typically report significant group effects despite the variability demonstrated among participants, with some showing clear, meaningful improvement, while others only show statistical improvement or none at all. These variable results may be related to the conventional stimulation intensity level of 2mA. Recent evidence suggests an electric field of at least one v/m is needed to affect local networks in the brain [15] reliably. However, tDCS at 2mA produces an electric field around only 0.6 v/m because a large amount of shunting (a dilution of the incoming current) occurs as the current travels from the electrode on the scalp, through the skin, skull, and cerebral spinal fluid (CSF), before reaching the brain. The most direct way to increase the electric field produced in the brain is to increase the intensity delivered. Current tDCS machines can have an intensity level of 4mA, resulting in more substantial electric fields than one v/m. We predict that if we were to administer tDCS at 4.0 mA, a more significant number of participants would show a meaningful response, and those who improve at 2mA may improve even more from 4.0mA due to having a larger electric field produced.

We aim to test this hypothesis in people with Alzheimer's Disease because they have unique attributes that may impact tDCS differently from other populations. More specifically, the amount of shunting is predicted to be larger due to increasing CSF from brain atrophy [16]. Thus, 2mA may be too weak to be very effective in some people with Alzheimer's Disease due to the higher level of shunting. More significant improvements would be observed from a higher intensity level that can

better interact with the remaining cortex. Alzheimer's Disease is also predominately female, and past studies have suggested men and women respond differently to tDCS [17-24]. For example, women have smaller skulls than men in general, which are predicted to receive more of the incoming stimulation. Finally, as Alzheimer's Disease is progressive, the degree of impairment may be relevant [25]. We will check if individuals who are more impaired benefit more when the stimulation intensity is set higher. The level of impairment will be measured in two ways: (1) the baseline score on the task training in the study (baseline severity); and (2) scores collected from cognitive testing (cognitive severity).

Purpose of the Research

Demonstrating results are possible with 4 mA, which may be superior or unachievable with 2 mA, would persuade other researchers to also explore if the improvement (or the lack thereof) in their own tDCS studies would be present or larger using 4 mA tDCS. Over time, just as tDCS researchers began favouring 2 mA over lower intensity levels, 4 mA rather than 2 mA could become the new convention. Also, by exploring how individual differences impact the response observed, we can target those individuals who are expected to most benefit from tDCS. In this manner, tDCS studies can become more efficient.

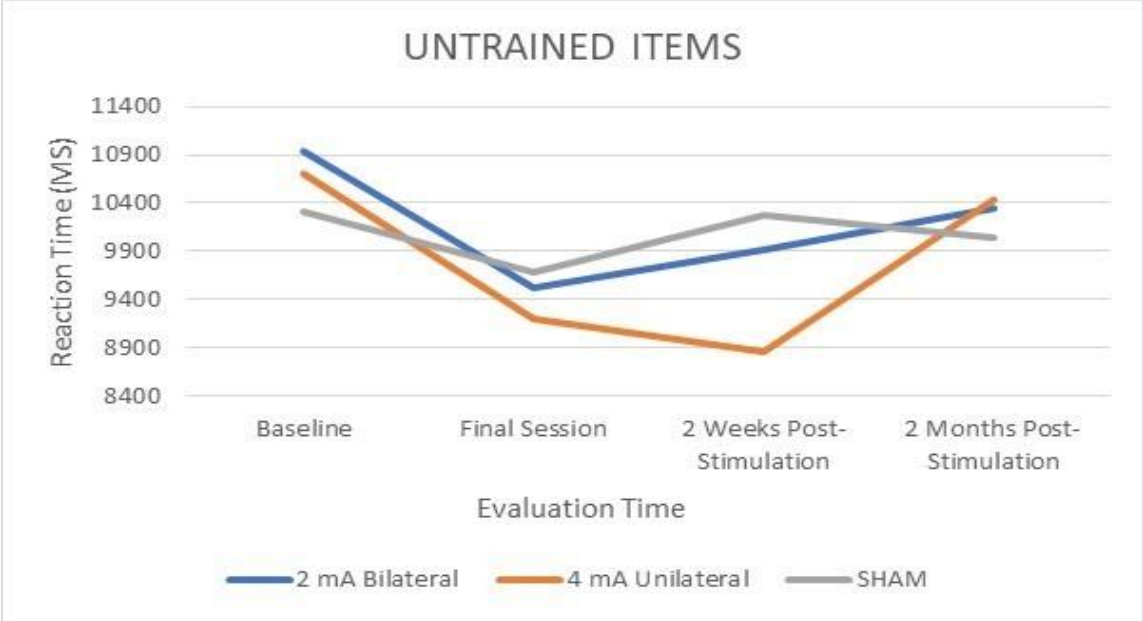
Hypotheses Addressed

- The degree of improvement observed in people with Alzheimer's disease will be significantly greater when training is carried out at higher stimulation intensity (4mA vs. 2mA, SHAM).
- There will be significantly more significant improvement observed when:
    1. individuals have more atrophy (decreased brain volume, higher CSF volume).
    2. Individuals have a higher degree of impairment.
    3. The participant is female.

PRELIMINARY STUDIES

The proposed study models after our original three-round study [5] where three different tDCS montages were compared for improving naming ability. We recently completed another three-round study [31] where a mixed group of people with dementia (AD and FTD) concluded three consecutive rounds of executive function training with either: 4mA tDCS targeted towards the left dorsolateral prefrontal cortex (DLPFC), 2mA tDCS via two anode electrodes to the left and right DLPC respectively, or SHAM stimulation, which is the accepted placebo condition in tDCS studies. In SHAM stimulation, tDCS is only briefly active at the beginning and end of the session, which mimics the real-life sensation of tDCS as feelings are felt mainly only at the beginning and end of the session when the current is ramping up or down. We measured how much participants improved on an N-Back task, defined as having faster response times. For evaluation, participants completed two versions of this N-Back task: one practiced during the tDCS sessions, and another never practiced and was only given during evaluations. For trained items, results were similar regardless of stimulation condition, but the most significant improvement was found for the 4mA condition for untrained items.

Because the bilateral montage delivered 2mA to each anode electrode over the left and right DLPC, finding superior results for the unilateral 4mA condition could be related to the involvement of the right DLPFC being stimulated, or due to a stronger intensity level being administered. The study proposed here will investigate the latter hypothesis: results were due to a more vigorous tDCS intensity (i.e., 4mA).



METHODS:

Sample

Based on pilot data, we expect a pooled standard deviation for response time on the N-Back test of 3,000 ms and a correlation of 0.89 between adjacent time points (pre, post, follow up). For 80% power to detect a difference across the three levels of intensity, while also accounting for the sex of a participant, a repeated-measures ANOVA test at an alpha level of 5% will require 54 participants with AD (27 men and 27 women). To compensate for anticipated attrition over the study, we will recruit a sample of 30 men and 30 women, 60 total, randomized into the three treatment arms. These participants would have received the diagnosis of probable AD from Baycrest's Memory Clinic expert staff [32, 33] according to standard clinical criteria. Only patients with no family history of epilepsy and who can give consent will be tested. We will seek people with mild to moderate AD (Reisberg stages 3, 4, or 5, [34]). Participants must show no history of stroke or traumatic brain injury, nor shunts or metal in the head that could interfere with the delivery of tDCS. Finally, people will have no evidence of significant heart disease, alcoholism, drug use. All

enrolled participants will be expected to complete an MRI; however, if they are unable to complete an MRI due to the presence of an exclusion criterion, they will still be allowed to complete all subsequent stages of the study. In the initial assessment, we will verify participants can complete the study task (N-Back). Only individuals able to complete this task will be allowed to complete the study.

Recruitment and Pre-Assessment

All participants are recruited following the same enrollment protocol: Initial contact, screening, and pre-assessment. For *the initial contact*, the research coordinator will receive names of potential participants from the Clinical Trials Unit at Baycrest. The files of these individuals will be acquired from Sam & Ida Ross's Memory Clinic. Their contact information and diagnosis will be noted. They will then be contacted using a prepared telephone script. Those individuals who show interest in the study will then be scheduled a screening with Dr. Carlos Tyler Roncero.

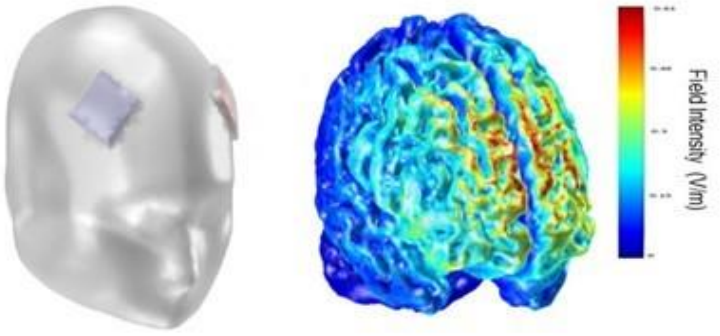
This *screening* can be done in person at Baycrest, or virtually over Zoom, and the participants can choose a particular modality if they have a preference. During the screening, Dr. Roncero will go over the consent form with the participant, including the mechanics, history, and side-effects of tDCS, and the planned study design (i.e., what participation would entail schedule-wise). The screening also allows Dr. Roncero to evaluate subjectively if the person may be too impaired for the study (for example, if they are unable to communicate or answer questions during the screening). If this scenario were to arise, Dr. Roncero would explain to the participant, and presumed caregiver, that the person is too impaired for the study. The screening is also an opportunity for the potential participant to ask any questions they might have. Assuming the participant is agreeable to participating in the study, a pre-assessment will be scheduled.

In this *pre-assessment*, the participant will be asked to complete versions of the tasks that will be administered during the study. In this manner, we can further verify that the potential participant is a good candidate for completing the study. Assuming they are able to successfully complete the tasks during the pre-assessment, and continued to be interested in participation, he or she would then be formally enrolled and scheduled into the study. Otherwise, the participant would be explained that they are unable to be enrolled into the study because they are unable to successfully complete the tasks planned. Because tDCS is an interactive therapy (a targeted behaviour must occur while the stimulation is administered), it is crucial that participants be able to complete the planned tasks, and simply receiving tDCS passively (i.e., while doing nothing) would be largely, if not completely, ineffective.

tDCS Parameters

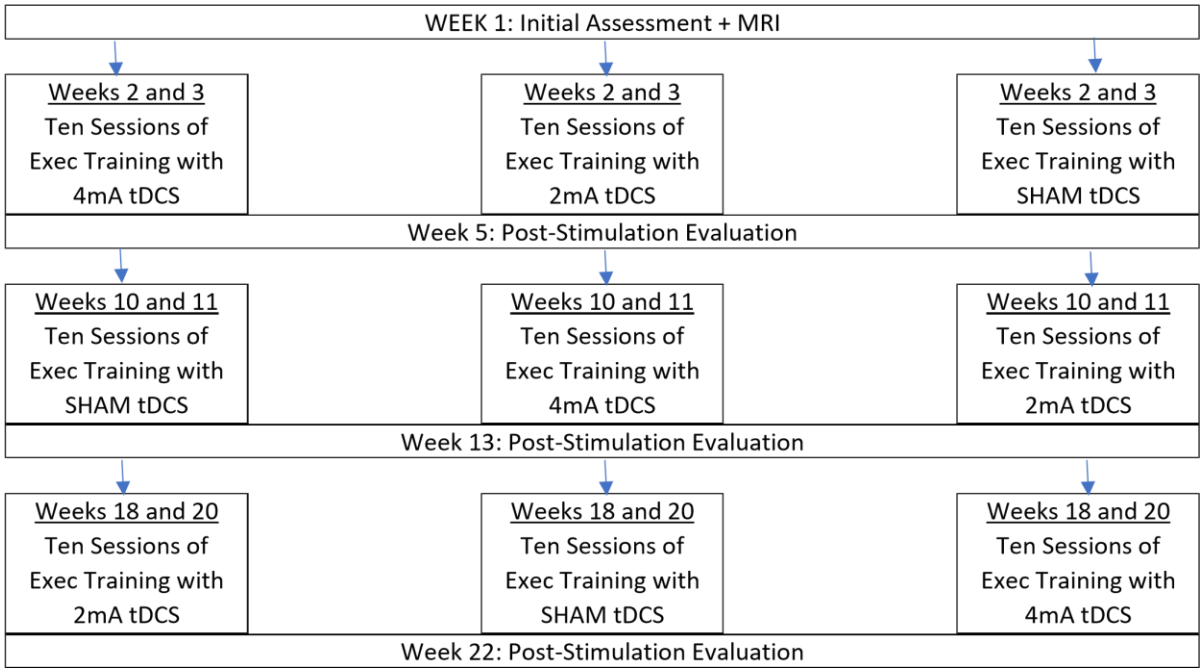
Stimulation will be delivered for 20 minutes concurrent with the beginning of the session, with the anode electrode placed over the left DLPC and the cathode over the right DLPC.

Figure 1 (below). *Dorsolateral Prefrontal Cortex Montage.* Activation prediction based on modeling software from Soterix HD-Explore; color gradients reflect increasing levels of predicted intensity, where red reflects a peak intensity of 0.61 mA.



Study Design

Participants will be randomized into three treatment arms. Participants will complete three rounds of executive function training in each arm, with each round paired with different stimulation intensity (SHAM, 2mA, 4mA). The below flowchart displays the procedure that participants will follow:



Initial Assessment

In the first week, all participants will receive an initial assessment to gather demographic information (age, sex, years of education, racial background, and hand preference) and conduct a formal evaluation of participants. Evaluation includes the Montreal Cognitive Assessment (MoCA; [26]) and the Mini-Mental State Exam (MMSE; [27]) to assess the level of cognitive function, as well as a practice version of the study task (N-Back) where they must state via a button press on a computer if the presented image is the same or different from the previous image. This is to ensure the participants can complete it in the upcoming study rounds. From these tasks, participants' impairment scores will be calculated. *Cognitive severity* will be measured as the combined total from the MoCA and MMSE (x/30 + x/30). In contrast, *baseline severity* will be measured as the

average response time on the practice version of the N-Back. Assuming inclusion criteria are met, participants in the first week will also complete a structural MRI [view MRI protocol – page 11]. We will use SPM 12 to quantify head and tissue layers, including CSF, which will be quantified relative to the participant's skull size. For skull thickness and grey matter, we will quantity regions around the left DLPFC.

Baseline Evaluation

Neither the evaluators nor the participants will be told if the tDCS they received during the training sessions was 2mA, 4mA, or SHAM. Therefore, the study will be double-blind. The first evaluation will take place right before the first training session begins. Two versions of the N-Back task (described later) will be administered: one that will be trained in the upcoming round and one that will never be trained. Evaluating performance on trained and untrained lists allows us to examine the impact of tDCS on training and how well this improvement generalizes to an untrained version, indicating a more global improvement. To determine if the executive function training has any additional generalized effects, we will also administer the following tasks to participants during evaluation to check for improvement in the following domains: General Cognitive Status, as measured by the MoCA and MMSE, Verbal Fluency, as measured by letter fluency tests (letters FAS) from Dellis-Kaplan executive function system (D-KEFS, [37]); Mood, assessed by the Geriatric Depression Scale (GDS, [38]); Short-Term Memory, measured by a traditional Corsi Block task [39] and a digit span forward and backward from Wechsler adult intelligence scale [40]]. These tasks are exploratory to check for generalized improvement.

Training Sessions

All training sessions will have the same format and involve the administration of tDCS combined with training. More specifically, during the first 20 minutes, a research participant will

give sham or tDCS set at 2mA or 4mA for 20 minutes and will remain during the session with the participant for safety precautions and troubleshoot any computer problems. Simultaneously with the stimulation, participants will use the computer to practice the given N-back task. This N-back task is modeled off of the 1-back version of the N-back Matching Task [41]. In that study, participants were asked whether a presented digit (e.g., a red 5) was the same as the previously shown digit (either a red five or some other number-color combination); they gave their response by pressing a key on a keyboard to indicate if the number is the same (i.e., a red 5), or different (i.e., something other than a red 5). Following Basak and O'Connell [42], we have created different versions of this task but use images (animals, fruits, vehicles, faces) rather than numbers to make the task slightly easier for people living with dementia. The only difference between these versions is the stimuli presented. We also have normed these versions with normal elderly controls and found that response times and errors were similar for all versions. In each round, participants will practice a different version of the N-Back. Evaluations specific to that round will also administer a round-specific untrained list.

Subsequent Evaluations

For each round, in addition to the evaluation just before the first stimulation session, an additional evaluation will take place during the final training session, and two weeks later after the final session. In this manner, we can obtain a baseline measurement, check for post-stimulation changes, and if those changes have continued two-week's post-stimulation.

Structural MRI Protocol

Participants will undergo a Structural MRI at Baycrest. The protocol has been informed to the MR Technicians (please see attached documents). The Project Coordinator will book the MR suite using the Baycrest MR Web Scheduler with a 72 hour notice at the least.

Participants will be asked to arrive 15 minutes before their scheduled scan to review and fill the consent and MR screening forms. The participant will then be escorted to the Interview room to be interviewed by a Level 11 MR Personnel with respect to their MR screening form and medical history prior to changing for the MR exam. After changing, the MR technologist will escort the research participant into the magnet room and the accompanying researcher (Assistant, Coordinator or PI) to the control area. Post scanning, the lab member accompanying the research participant will monitor the change process, and other processes outlined in the "MR Research Suite Process Bacycrest – RRI."

To be able to successfully perform the MRI, lab members will undergo the Virtual MR Safety Training & Orientation session and will also receive an in person suite tour.

Planned Analyses

The primary outcome measure will be improvement on an N-Back Task, both a trained version and an untrained version. Improvement will be measured in terms of the average response time (i.e., the amount of time needed to make a response). A repeated-measures ANOVA will be run to compare the three stimulation conditions (SHAM, 2mA, 4mA) with sex (male, female) as a between-subject variable. This analysis will be conducted separately for the trained and untrained items. Scheffé tests will compare the different conditions. We expect to find the greatest improvement in the 4mA condition.

Next, we will calculate a tDCS time improvement score for each participant per condition: the difference between the final average response time on the N-Back task from the last stimulation session subtracted from the baseline response time in each condition. To produce tDCS *effectiveness scores*, the time improvement score in the SHAM round will be deducted from the number calculated in each real tDCS round. In other words:

• Time Improvement in the 4mA condition *minus* Time improvement in the SHAM condition;

• Time Improvement in the 2mA condition *minus* Time improvement in the SHAM condition.

Thus, a tDCS effectiveness score is calculated for each participant in the 4mA and 2mA conditions. These tDCS effectiveness scores will then be the dependent variables in a multivariate logistic regression; once for trained items, again for untrained items. The predictors will be the CSF level of a participant, grey matter volumes and skull thickness around the DLPFC, impairment scores (baseline and cognitive severity), and interactive terms representing the sex of the participant. In this manner, we can examine what individual differences predict the tDCS response in people with AD and if these predictors are the same for two and 4mA tDCS while checking for sex differences. We expect more significant levels of CSF, less DLPFC grey matter, thicker skulls, and greater impairment levels will be predictive of more substantial improvement in the 4mA condition. CSF and grey matter values may be less predictive for how well women respond to tDCS as their relatively smaller heads could compensate for increased shunting levels.

Finally, a 2 (male AD, female AD) x3 (4mA, 2mA, SHAM) between-subject repeated measures ANOVA will be run for tasks administered in evaluation: MoCA scores, to check for changes in general cognition, as well as for verbal fluency, digit span, and Corsi to check for generalized executive function differences. These analyses are exploratory.

Funding

This study is supported by BrightFocus Foundation, which reviewed the submitted protocol, and awarded funds to Dr. Carlos Tyler Roncero towards completing the proposed study.

Risks

The tDCS protocol for this experiment was determined according to the best practices observed in previous research using tDCS stimulation [45]. Furthermore, tDCS is safe, has virtually no side effects,

is technically easy to carry out, and is not uncomfortable to undergo [46,47]. Multiple studies have also reported that the administration of 4 ma tDCS has no more adverse effects than 2 ma tDCS [48]. No incidence of seizure has been recorded, although side effects could include headache, drowsiness, itching sensation, nausea, and, in rare cases, disorientation. In our experiences, the only observed and reported side-effect has been temporary redness post-stimulation where the sponge was placed, as well as the occasionally reported headache.

If the event were to result in lasting pain and hospitalization, then it would be reported as a 'Serious Adverse Event" and full details would be noted to the research ethics board as well as Health Canada. These events would be recorded on the worksheets being used to collect the rest of the data. We must stress, however, that after administering 4 mA tDCS to around 60 participants, for hundreds of tDCS sessions, we have never encountered any such event. Although we have safety protocols in place for any encountered adverse or severe adverse events, we believe such events will fail to occur in the present study.

Confidentiality

A research study file as well as medical records identifying participants will be maintained within Dr. Howard Chertkow's lab. Names and identifying information will be replaced with a code, and the information will be kept on file for 10 years after the end of the study. Data collected from participants' who withdraw from the study will also be kept, unless participants withdraw consent for its use.

Communication and Publication of Research Results

The found results may be presented at research conferences and written up in a manuscript submitted for a publication in a respected science journal. The data will never be used for commercial goals and all participant information will remain confidential. Individual's participant data will be presented using a code (e.g., Participant 1), which ensures no reader of the data could identify the participant. The results found can also be used to back-up further studies involving 4 mA tDCS because

we will be able to present formal data demonstrating its effectiveness compared to other intensities of stimulation (SHAM, 2mA) in people with Alzheimer‘s Disease.

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