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Research Study Title: Investigating if a stronger tDCS intensity is more effective for improving naming ability in people living with Alzheimer's Disease

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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]. We have shown that anomia (picture naming deficits) is improved with seven to ten daily half-hour sessions of tDCS along with language training, for both AD and FTD [3-7, 28, 32-34], with effects lasting several weeks.

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 a naming task (baseline severity); and (2) scores collected from cognitive testing (cognitive severity).

Purpose of the Research

tDCS has the potential to emerge an effective ancillary symptomatic therapy for Alzheimer's Disease. However, the optimal tDCS parameters are unknown, improvement varies from person to person, and we cannot presently predict who will most benefit from tDCS. The proposed project aims to fill this knowledge gap by investigating how different variables impact the effectiveness of tDCS. In this manner, the proposed project will provide a significant step forward towards finding the optimal participants for treatment as well as the optimal tDCS delivery method for people with AD. This work, using a proven naming task, is an essential step towards future random clinical trials investigating tDCS as therapy for people with AD.

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:

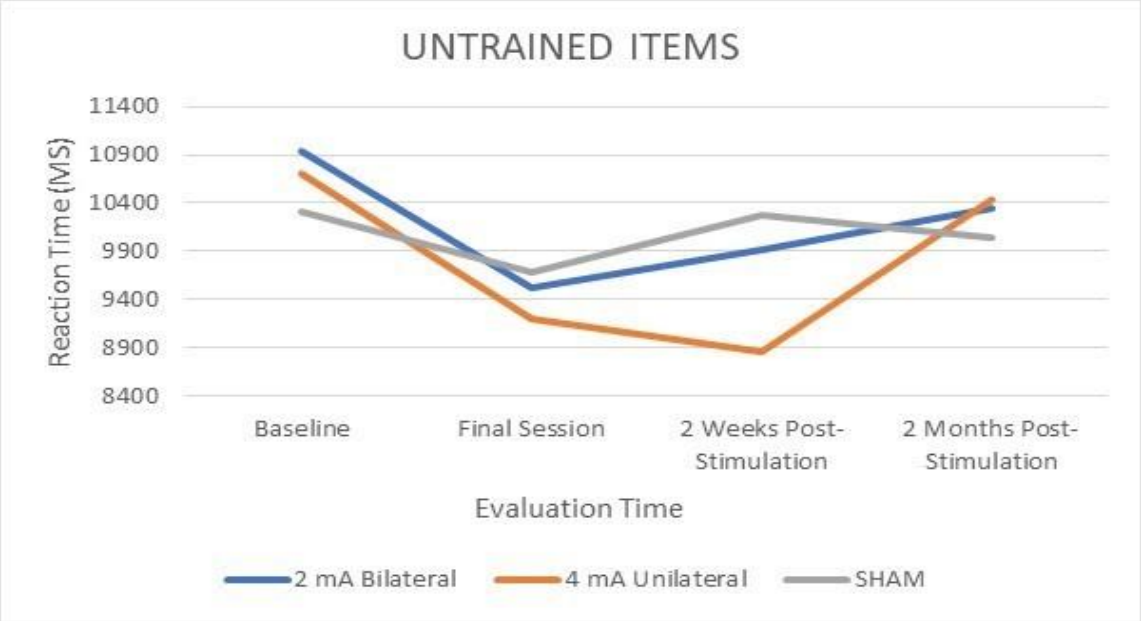
1. Individuals have more atrophy (decreased brain volume, higher CSF volume).
2. Individuals have a higher degree of impairment
3. The participant is female (possibly due to skull differences).

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 [28] 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 for untrained items, the largest improvement was found for 4mA tDCS (see Figure 1 below). 4 mA tDCS was also well tolerated with no adverse effects among the 24 individuals who participated. Building on this work, we now propose to carry out a training

paradigm to compare 4 mA, 2 mA, or SHAM, but using picture naming, a domain we have already shown to improve with tDCS in our previous studies [4-6], with tDCS again targeting the Inferior Parietal Lobe (IPL).

Figure 1:



METHODS:

Sample

Based on the previous study where tDCS was used for language training [6], we expect a partial eta square around 0.20. 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.

These participants would have received the diagnosis of probable AD from Baycrest's Memory Clinic expert staff [29, 30] 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]) who score between 18 and 25 on the MoCA [26]. 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. Participants will be evaluated and trained using different naming lists each round. We have developed equivalent versions of these naming lists in our lab, which allows us to use a different trained and untrained list each round.

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

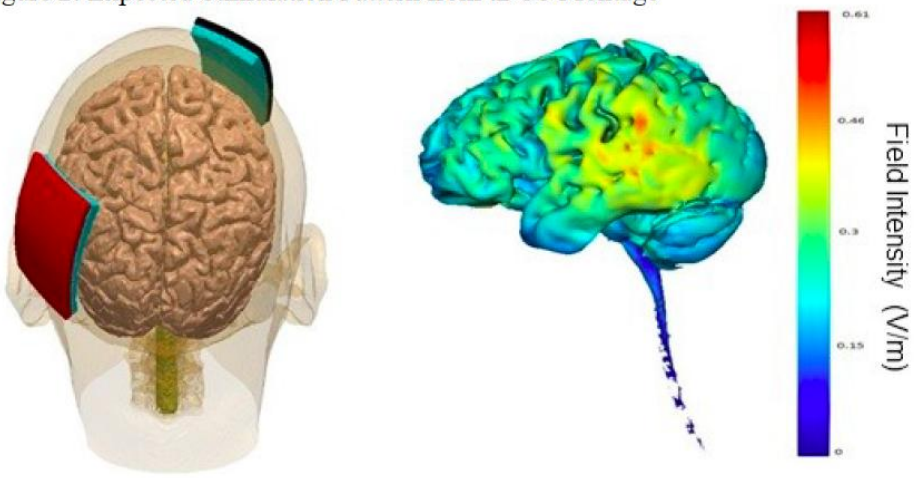
presumed caregiver, that the person is too impaired for the study. The screening is also an opportunity for the potential participant to ask any questions they might have. Assuming the participant is agreeable to participating in the study, a pre-assessment will be scheduled.

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

As done in our previous three-round study where naming training was paired with tDCS [5], stimulation will last for 20 minutes, concurrent with the beginning of the session. The anode electrode placed will again be placed over the IPL and the cathode over the right supraorbital region. Figure 2 shows the expected stimulation pattern.

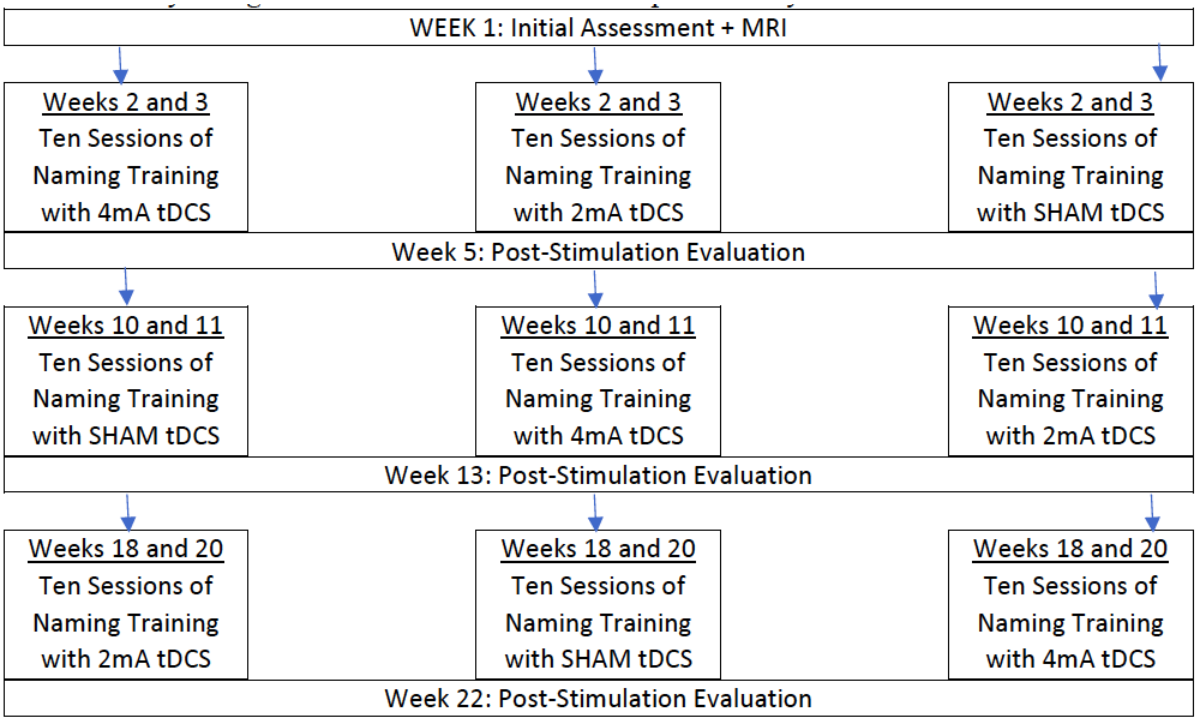
Figure 2: Expected Stimulation Pattern from tDCS Montage



View from Back Activation Prediction

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. The Naming Task of the Cambridge Semantic Battery will be given to verify the presence of anomia (an inclusion criterion of the study). 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 score obtained on this naming task. 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 calculate a person's skull thickness and grey matter volumes around the IPL, as well as the CSF level, which will be quantified relative to the overall skull size of the participant.

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 session of each round will consist of a baseline evaluation prior to the training session where participants will be asked to name presented images from two lists: one that will be subsequently trained that round, and a second list that will be left untrained. By administering two lists during evaluation, one trained, one untrained, we can examine the impact of tDCS on training, and if this improvement generalizes to an untrained naming list. General Cognitive Status, as measured by the MoCA and MMSE. Mood, assessed by the Geriatric Depression Scale (GDS, [35]).

Training Sessions

The language training protocol will be the same we have previously published [5], which successfully improved naming in people with dementia. 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. After a research assistant has set up the tDCS machine and started stimulation, the participant is presented 45 images (from Snodgrass and Vanderwart; [31]) individually on a laptop, one by one, and asked to name each item that appears. Items have a range of difficulty and familiarity, which ensures it can be used for participants with different levels of impairment; perfect scores and scores of zero are unexpected. The research assistant notes which items were incorrectly named. These misnamed images will then be ranked in familiarity from the most familiar to the least familiar, based on norms collected in our lab. The five most familiar missed items will form a five-item study group. The trainer then presents each item of the study group one by one to the participant, naming each item in front of the participant. Next, the five images are presented one by one again,

but now the participant is asked to name them. When participants have difficulty remembering the name of the item, the trainer will give phonological cues (starts with a . . .) or semantic cues (In Halloween, you carve a . . .). This group of items is then shown again one by one a second and a third time, each time noting if the participant can correctly name it.

After the study group is presented three times, those items correctly named by the participant three times in a row without cues are replaced with the next most familiar item that was missed at the beginning of the session. Thus, when the study group is presented a fourth time, it contains images that the participant still hasn't named three times in a row or new items that replaced ones named three times in a row. The training session will continue in this manner, replacing items named three times in a row, maintaining those yet to be named successfully three times, until all items missed at the beginning of the session are incorporated into the study group and trained with the participant.

In summary, training sessions have participants practice picture naming, as might occur in a typical speech therapy session for anomia, except the first 20 minutes are concurrent with tDCS, which is typical in tDCS studies. Most sessions will last around an hour. Due to the training involved, we expect participants will improve regardless of the stimulation condition but predict this improvement will be larger when done with real tDCS, and largest when done with 4mA tDCS. Related to this, we will check if this superiority of 4 mA over 2 mA is related to a participant's condition (e.g., sex, level of atrophy).

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 the naming lists administered, both a trained version and an untrained version. Improvement will be measured in terms of the number

of images correctly named post-training compared to baseline. 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. We expect to find the greatest improvement in the 4mA condition.

Next, we will calculate how much a participant improved in each condition by taking the naming score obtained at baseline for a naming list and subtracting it from the naming score obtained in the final stimulation session (e.g., 32 (final) – _20 (baseline) = an improvement score of 12). These scores are then used to produce tDCS effectiveness scores: the improvement score in the 4mA condition minus the improvement score in the SHAM condition; and the improvement score in the 2mA condition minus the improvement score in the SHAM condition. These tDCS effectiveness scores will then be the dependent variables in a multivariate logistic regression; once for trained items, one for untrained items. The predictors will be the CSF level of a participant, grey matter volumes and skull thickness around the IPL, 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 2mA and 4mA tDCS, while checking for sex differences. We expect more significant levels of CSF, less IPL grey matter, thicker skulls, and greater impairment levels will be predictive of more substantial improvement in the 4mA condition because this stimulation intensity is needed to compensate for higher levels of shunting and severity. 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.

Funding

This study is supported by the Alzheimer's Scoiety, 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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