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Transcranial Direct Current Stimulation for patients with Alzheimer's Disease

Exploring the influence of different stimulation parameters on treatment success

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Abbreviations

AD	Alzheimer’s disease
CSF	Cerebrospinal fluid
DLPFC	Dorsolateral prefrontal cortex
DTI	Diffusion tensor imaging
ECT	Electro Convulsive Therapy
EEG	Electroencephalogram
EF	Electric field
FA	Fractional anisotropy
FDA	U.S. Food & Drug Administration
FDG-PET	PET imaging tracing glucose uptake in the brain
FEM	Finite Element Method
FMIN	Forceps minor
GABA	Gamma-aminobutyric acid
GLM	Generalized Linear Model
HD-tDCS	High-definition tDCS
MCI	Mild Cognitive Impairment
MD	Mean diffusivity
MMSE	Mini Mental Status Examination
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy

NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke Alzheimer Disease and Related Disorders Association
NMDA	N-methyl-D-aspartate
lATRleft	Left anterior thalamic radiation
LTP	Long term potentiation
lCCG	Left cingulum cingular bundle
PALM	Permutation Analysis of Linear Models
PET	Position emission tomography
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	Randomized controlled trial
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
TMT	Trail Making Test
TRACULA	TRActs Constrained by UnderLying Anatomy

List of papers

Paper I Rasmussen, I. D., Boayue, N. M., Mittner, M., Bystad, M., Grønli, O. K., Vangberg, T. R., Csifcsák, G., & Aslaksen, P. M. (2021). High-Definition Transcranial Direct Current Stimulation Improves Delayed Memory in Alzheimer's Disease Patients: A Pilot Study Using Computational Modeling to Optimize Electrode Position. *J Alzheimers Dis*, 83(2), 753-769. https://doi.org/10.3233/jad-210378.

Paper II: Rasmussen, I. D., Mittner, M., Boayue, N. M., Csifcsák, G., & Aslaksen, P. M. (2023). Tracking the current in the Alzheimer's brain - Systematic differences between patients and healthy controls in the electric field induced by tDCS. *Neuroimage: Reports*, 3(2), 100172. https://doi.org/https://doi.org/10.1016/j.ynirp.2023.100172.

Paper III Grønli, O. K., Daae Rasmussen, I., Aslaksen, P. M., & Bystad, M. (2022). A four-month home-based tDCS study on patients with Alzheimer's disease. *Neurocase*, 28(3), 276-282. https://doi.org/10.1080/13554794.2022.2100710.

Abstract

Background: Transcranial direct current stimulation (tDCS) is a potential symptom-revealing treatment for Alzheimer's disease. Even though promising, the results of clinicals studies are mixed. Computational modeling simulates the electric field using magnetic resonance imaging (MRI), quantifying the intensity and density of the current reaching desired brain regions. The traditional tDCS device is bipolar, with one anode and one cathode electrode. High-definition tDCS (HD-tDCS) provides higher precision in targeting specific brain regions. tDCS needs to be both tolerable and feasible to be implemented in clinical practice. The device is portable, opening the possibility of treating patients in their homes.

Aims: This thesis explored how electrode placement, frequency, and inter-individual differences in brain anatomy influence tDCS- treatment.

Methods: In Paper I, 19 Alzheimer's patients were randomly assigned to receive either active or sham HD- tDCS. MRI was collected from all participants, and SimNIBS was used to simulate tDCS-induced current, choosing the montage with the highest anodal current strength in the left dorsolateral prefrontal cortex. In Paper II, MRI data from 24 Alzheimer's patients and 24 controls were collected from the XNAT database. SimNIBS was used to study how tDCS-induced electric current was affected by disease related atrophy. Paper III explored the effect, feasibility, and tolerability of everyday use of bipolar tDCS at home.

Results: In Paper I, delayed memory improved after active HD-tDCS. A significant positive correlation was found between preserved white matter and improvement in delayed memory. In Paper II, the electric field caused by tDCS was weaker and more widespread for the Alzheimer's group compared to the control group. HD-tDCS montages produced more focal stimulation than bipolar montages. In Paper III, daily tDCS sessions at home were feasible and tolerable.

Discussion: The results are promising for the implementation of HD-tDCS and home- based treatment for Alzheimer's patients. Computational modeling has emphasized the need of developing specialized protocols to this patient group. The small sample sizes pose challenges to the generalizability and reproducibility of the findings. The research is of clinical relevance in terms of optimizing tDCS treatment for Alzheimer's disease. It is important to conduct larger, well-designed studies for more robust evidence on potential benefits and limitations of tDCS.

Sammendrag

Bakgrunn: Transkraniell likestrømsstimulering (tDCS) er en potensiell symptomlindrende behandling for Alzheimers sykdom. Selv om resultatene fra kliniske studier har vært lovende, er de også varierende. Ved hjelp av magnetisk resonansavbildning (MR) kan man simulere den tDCS- induserte strømmen i ulike hjerneregioner. Den tradisjonelle tDCS-enheten er bipolar og består av en anode og en katode elektrode. Høydefinisjons tDCS (HD-tDCS) gir bedre presisjon for å nå spesifikke hjerneregioner. tDCS må være gjennomførbar for å kunne implementeres i klinisk praksis. Utstyret er bærbart, noe som åpner opp for muligheten for hjemmebehandling.

Mål: Denne avhandlingen utforsket hvordan plassering av elektroder, frekvens og interindividuelle forskjeller i hjernens anatomi påvirket tDCS-behandling.

Metoder: I Artikkel I ble 19 pasienter med Alzheimers sykdom tilfeldig fordelt i en aktiv og en placebo HD-tDCS-gruppe. MR-data ble samlet inn fra alle deltakerne, og SimNIBS ble brukt til å simulere den tDCS-induserte strømmen. Elektrodeplasseringen som ga høyest anodal strømstyrke i venstre dorsolaterale prefrontale cortex ble valgt. I Artikkel II ble MR-data fra 24 Alzheimers pasienter og 24 kontroller samlet inn fra XNAT-databasen. SimNIBS ble brukt for å studere hvordan tDCS-indusert elektrisk strøm ble påvirket av sykdomsrelatert atrofi. Studie III undersøkte om hjemmebasert bipolar tDCS var gjennomførbart og tolererbart, der åtte Alzheimers pasienter mottok daglig stimulering over en fire måneders periode.

Resultater: I Studie I ble utsatt hukommelse forbedret etter aktiv HD-tDCS. Det ble funnet en signifikant positiv korrelasjon mellom bevart hvit substans og forbedring i utsatt hukommelse. Studie II viste at det elektriske feltet forårsaket av tDCS var svakere og mer utbredt i Alzheimer-gruppen sammenlignet med kontrollgruppen. HD-tDCS produserte mer fokal stimulering enn bipolar tDCS. I Studie III var daglige tDCS-økter hjemme gjennomførbare og tolererbare.

Diskusjon: Resultatene er lovende for å tilby HD-tDCS og hjemmebasert behandling til Alzheimers pasienter. Resultatene fra strøm simuleringen støtter behovet for spesialiserte protokoller for denne pasientgruppen. De små utvalgsstørrelsene i de kliniske studiene utfordrer generaliserbarheten. Forskningen har klinisk relevans når det gjelder optimalisering av tDCS- behandlinger.

1. Introduction

Alzheimer's disease (AD) is a progressive disease with increasing cases worldwide due to longer life expectancy. AD causes atrophy in the brain and disrupts neuronal activity. Transcranial direct current stimulation (tDCS) has emerged in the last two decades as a promising non-invasive brain stimulation technique (Nitsche & Paulus, 2000). A weak direct electric current is applied to the scalp via electrodes, causing modulation of cortical activity. TDCS can have a positive effect on patients' cognition by increasing neuronal activity (Nitsche & Paulus, 2000). The equipment is cheap, easy to use, and has few side effects (Lefaucheur & Wendling, 2019).

While offering stimulation to healthy individuals raises several ethical concerns (Day et al., 2022; Wurzman et al., 2016), treating patients who suffer from maladaptive neuronal activity can have a huge impact on both the individual and socioeconomic level (Majdi et al., 2022). Major limitations in tDCS research are inconsistent findings and low reproducibility (Lefaucheur et al., 2017; Woods et al., 2016).

The electric current penetrates the scalp, skull, meningeal membranes, and cerebrospinal fluid before creating an electric field (EF) in the cortex. These tissues have different conductivity properties, causing different EF distributions in the brain (Datta et al., 2009). Human brain-imaging techniques make it possible to track the current more precisely, predicting what areas are stimulated and at what strength. While pharmaceutical medication doses are individualized, tDCS procedures often place electrodes at the same coordinates on the skull, without considering the anatomical differences in the cortex (Hunold et al., 2023).

This thesis focuses on both anatomical differences between AD patients (Paper I) and a comparison between AD patients and healthy matched controls across different tDCS montages (Paper II). In Paper I, electrode positions were optimized using computational modeling, choosing the electrode montage for each AD patient with the "best fit," according to individuals' brain anatomy.

To be able to translate research into clinical practice, treatment must be feasible. tDCS is often provided in a hospital or university setting, which can be demanding for both patients and their caregivers (Valiengo et al., 2013). Paper III is a patient series exploring the possibility of delivering tDCS at home. Combined, these three tDCS papers on AD patients explore different stimulation parameters and their influence on treatment success.

2. Background

2.1. Alzheimer's disease

The first systematically researched case of AD was a woman in her 50s struggling with memory decline. After her death in 1906, Alois Alzheimer, a German psychiatrist, examined her brain by autopsy and discovered several brain abnormalities: The cerebral cortex was thinner than normal; senile plaques were present, along with intraneural fibrils and changes in glial cells (Hippius & Neundörfer, 2003; Selkoe, 2011). The disease was named Alzheimer's by Kraepelin in 1910, and today, after more than 100 years, neurofibrillary tangles and amyloid plaques are still the most recognized diagnostic parameters of the disease (Raskin et al., 2015). AD is a neurodegenerative disorder associated with widespread neuronal death, primarily in the medial temporal lobes (Raskin et al., 2015). In recent years, white matter alterations, also reported in this first autopsy case, have received increased interest as an important diagnostic feature (Amlien & Fjell, 2014; Hippius & Neundörfer, 2003; Maurer et al., 1997).

AD accounts for over 60% of cases of dementia (Blennow et al., 2006), and the disease is further divided into early and late onset (before and after the age of 65, respectively) in the International Classification of Diseases, Tenth Revision, diagnostic criteria (World Health, 2004). The gene APOE-4 is linked to a higher risk of the disease and a faster cognitive decline in early-onset AD (Mormino et al., 2014). However, the biggest risk factor for AD is age (Farrer et al., 1997). With an increase in age, the number of people suffering from AD increases, with an incidence of over 76 in 1000 people aged 85 or older ("2014 Alzheimer's disease facts and figures," 2014). The disease is progressive with no cure, but some disease-modifying medications do exist (Cummings et al., 2016). Socioeconomic costs are huge and are expected to increase as the population grows older.

2.1.1. Symptoms

The typical form of AD is amnestic, where memory impairment is the primary feature. In the initial phase of the disease, episodic memory, which involves absorbing new information, encoding the information, and then storing it properly in the long-term memory, is affected (Cummings, 2004; Dubois et al., 2010). In addition, spatial navigation is one of the earliest symptoms of AD, resulting in patients getting lost in both familiar and unfamiliar locations (Coughlan et al., 2018). Later, as the disease progresses, the impairments also affect sematic memory and immediate recall, and in the late stages of AD, procedural memory is impaired.

Other cognitive domains such as executive functions, language, and visual skills are also impaired with disease progression.

Non-cognitive symptoms may also be present, such as changes in personality, wandering, agitation, and sleep abnormalities (Schachter & Davis, 2000). A common psychiatric symptom in the early stages of AD is apathy. AD is a progressive condition, and the first symptoms are often subtle and can be misinterpreted as stress or depressive symptoms. The amnestic subtype of AD can be detected in neuropsychological tests specifically measuring immediate recall and short- and long-delayed memory. When cognitive impairments influence a person's ability to independently operate in day-to-day situations or in the community, their condition is classified as AD (World Health, 2004).

2.1.2. Pathological changes in the brain

The exact neurobiological cause of AD is unknown. A common hypothesis is that the disease leads to an extensive loss of neurons due to plaques (beta-amyloid) and tangles (tau-proteins) in the brain (Kumar et al., 2021). AD is also associated with neuroinflammation, especially in the medial temporal cortex (Heneka et al., 2015). A loss of cholinergic neurons, resulting in a decrease in the amount of acetylcholine, is likely to contribute to the memory impairment and behavioral symptoms observed (Schliebs & Arendt, 2011). Some studies also show low levels of glutamate and a disruption of neuroplasticity in AD patients (Selkoe, 2002). In the patients, positron emission tomography imaging tracing glucose uptake in the brain (FDG-PET) shows decreased glucose uptake, which indicates impaired synaptic activity (Arendt, 2009; Chételat et al., 2005).

2.1.2.1. MRI and Alzheimer's disease

Magnetic resonance imaging (MRI) can identify different tissue parameters that reflect aspects of brain damage. For clinical assessment, repeated structural MRI scans can give important information about brain changes over time (Frisoni et al., 2010).

Structural MRI studies of AD patients show substantial loss of gray matter in the medial temporal cortex at the early stages of the disease, spreading to neocortical areas with disease progression (Frisoni et al., 2010). Gray matter loss in the hippocampal areas and the parahippocampal areas predicts conversion from mild cognitive impairment (MCI) to AD in later stages, especially in the left medial temporal lobe (Bozzali et al., 2016). More specifically, the first preclinical signs of atrophy start in the transentorhinal cortex and then spreads toward the hippocampus (Miller et al., 2015). When forming episodic memory, the

entorhinal cortex and the hippocampus are key structures located in the medial temporal lobe, with projections to almost all neocortical areas, where sensory input is first processed. The loss of these connections gives rise to clinical symptoms of episodic memory impairment. There is a strong correlation between brain atrophy and the severity of cognitive impairment (McKhann et al., 2011). Neuroimaging and lesion studies suggest that episodic memory-recall strategies in AD patients are facilitated by the prefrontal cortex, especially the dorsolateral prefrontal cortex (DLPFC) (Grady et al., 2003; Kumar et al., 2017).

Thinning of the entorhinal cortex is another important diagnostic feature in AD (Holland et al., 2012). Studies show a correlation between entorhinal thickness and disease severity in AD (Bakkour et al., 2009). In addition to these specific regions, AD brains have a decrease in total brain volume due to cortical thinning and gyral atrophy (Frisoni et al., 2010; Vemuri & Jack, 2010).

Diffusion tensor imaging (DTI) is a type of MRI technique used to study the microstructural organization of tissues, especially the white matter in the brain (Le Bihan, 2003). The white matter in the brain is important for coordinating communication between brain regions. DTI gives us the ability to visualize the white matter pathways by studying the direction and strength of water diffusion. White matter changes in AD show alteration in myelin and oligodendrocytes, axonal degeneration, and vascular pathologies (Sjöbeck et al., 2005), which can be present before gray matter atrophy (Gold et al., 2012). Disease severity is associated with the extent of white matter abnormalities. Reduced fractional anisotropy (FA) and increased mean diffusivity (MD) are the main findings of white matter abnormalities in AD patients (Bozzali et al., 2016).

2.1.2.2. AD pathology and plasticity

Despite similar brain pathology, patients with AD exhibit significant heterogeneity in the degree of cognitive symptoms they experience. The cognitive reserve model can explain this phenomenon, where plasticity mechanisms allow for a delay and/or reduction in dementia symptoms in some patients, even in the presence of neuropathology (Stern, 2012). Plasticity refers to the brain's ability to adapt to experiences and is crucial for learning and memory. In AD, the brain's ability to undergo neuroplastic changes is impaired, which contributes to the cognitive deficits seen in the disease (Selkoe, 2002). As AD progresses, damage to neural networks reduces neuronal plasticity (Kumar et al., 2017; Stern, 2012). Studies have shown

that, in early AD, plasticity can act as a compensatory mechanism by utilizing alternative networks and cognitive strategies to cope with brain pathology (Hill et al., 2011).

2.1.3. Existing treatment

AD has no known cure, but medication along with lifestyle and dietary modifications can delay its progression. Acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists are the most frequently used medications in AD, although they have limited efficacy and only temporarily improve cognitive symptoms for some patients (Huang et al., 2020; Mendiola-Precoma et al., 2016). In addition to pharmacological interventions, behavioral approaches can have a symptom-modifying effect. Cognitive behavioral therapy, exercise therapy, and music therapy can increase activities of daily living and reduce symptoms of depression (Na et al., 2019; Yiannopoulou & Papageorgiou, 2020). In line with acetylcholinesterase inhibitors and NMDA receptor antagonists, behavioral interventions are symptom-modifying and not disease-modifying treatments.

In June 2021, the U.S. Food and Drug Administration (FDA) approved aducanumab as a treatment for AD. Although clinical trials showed some uncertainties, it was concluded that the drug is likely to have clinical benefits for patients since it targets the underlying pathophysiology of AD by reducing amyloid beta plaques. This is the first AD treatment approved by the FDA since 2003. However, in December 2021, the European Medicines Agency recommended refusing the marketing authorization, and the company withdrew the application a few months later (https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/aduhelm). The clinical impact of aducanumab is still unknown.

Since AD is a complex disease with an uncertain cause, finding a cure is challenging (Cummings et al., 2016; Schneider et al., 2014). It may take decades to discover a cure, but it is crucial to search for treatment options that can improve the daily function and quality of life of AD patients by reducing symptoms.

2.2. TDCS to alter neuronal activity

The neuronal activity in the Alzheimer's brain is disrupted. By applying low-amplitude direct current to the brain through electrodes attached to the scalp, the firing of neurons may be manipulated. This section will first introduce brain stimulation and its history, and then focus on tDCS and its potential for treating AD symptoms.

2.2.1. Electric current with the intention to treat

The first description of using transcranial stimulation, according to Sarmiento et al. (2016), is from the 16th century, when a torpedo fish was used over the scalp to relieve headache in a patient (Sarmiento et al., 2016). In the 18th century, a direct current battery was generated by Galvani, who was one of the first to utilize direct current in clinical applications (Sarmiento et al., 2016). With new technology around the millennium, electric brain stimulation was investigated, exploring how the brain was influenced by the direct current (Priori, 2003). In the last two decades, there has been an increasing interest in brain stimulation and its potential for manipulating behavior and treating psychiatric and neurological diseases.

Today, there are several different approaches to brain stimulation, depending on the type of current delivered to the brain and whether the procedure is invasive or non-invasive. While invasive brain stimulation requires invasive surgery, non-invasive brain stimulation induces electric current to the brain by placing a coil or electrodes on the scalp. The two major modalities of non-invasive brain stimulation are transcranial magnetic stimulation (TMS) and tDCS. While TMS produces action potentials in underlying neuronal cortices, tDCS cannot independently, without afferent input, cause action potentials. The strength of the tDCS current, however, is enough to modulate neuronal firing by altering spontaneous and excitability activity of neurons (Lefaucheur & Wendling, 2019; Nitsche & Paulus, 2000).The advantages of tDCS in clinical settings are that the device is portable, easy to use, considered safe with few side effects, and is relatively low-cost compared to other brain stimulation techniques (Lefaucheur & Wendling, 2019). TDCS is not to be confused with electroconvulsive therapy (ECT). While tDCS delivers a low-intensity current, ECT involves a much higher-intensity electrical current (0.9–1.4 amperes), which is delivered to the brain to induce a seizure with the goal of treating severe mental illnesses such as major depression.

For tDCS, a number of computational modeling studies have demonstrated that even though a substantial amount of current is shunted on the scalp, skull, and cerebrospinal fluid (CSF), a sufficient dose for neuronal activity modulation penetrates these tissues and reaches gray matter (Fregni et al., 2021; Nitsche & Paulus, 2000). Neurophysiological evidence of tDCS effects has also been obtained in human studies using neuroimaging, single pulse TMS, and electroencephalogram (EEG) (Lang et al., 2005; Nitsche & Paulus, 2000; Priori et al., 1998).

TDCS studies have been carried out on a range of different psychiatric and neurological diseases, with most studies published on depression and stroke. Studies have also been

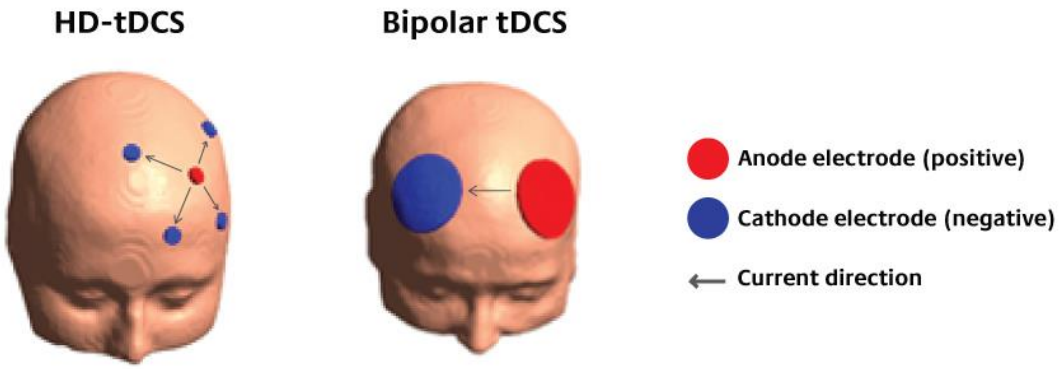
conducted on healthy participants, and a meta-analysis produced robust findings of enhancement of both cognitive and motor performance among aging participants (Summers et al., 2016). Studies show promising results for enhancing cognitive performance in patients with MCI (Meinzer et al., 2015).

When applying tDCS, two or more electrodes are placed on the scalp and connected to the battery-operated current generator. “Active” electrodes are located over the brain areas targeted for modulation, and “reference” electrodes are often placed in a brain area in the contralateral hemisphere or over the deltoid muscle. The number of electrodes varies, but the most common setup is one active and one reference electrode, known as bipolar, or conventional, tDCS. Another setup is HD-tDCS, where multiple electrodes are used, often in a ring formation, with one active electrode in the center, surrounded by four reference electrodes (Figure 1) (Datta et al., 2009; Villamar et al., 2013).

The most common current intensity when delivering tDCS is 1–2 milliamperes. The current flows from the anode (+) to the cathode (-) electrode, passing through the scalp and reaching the brain tissue underneath and between the two electrodes. A general assumption is that while anodal electrodes can enhance cortical activity, cathodal electrodes can suppress activity (Nitsche & Paulus, 2000). In bipolar montages, electrode sizes often vary between 25 and 35 cm², whereas HD-tDCS electrodes are usually smaller and around 1.2 cm in diameter.

Figure 1

Bipolar and HD-tDCS



tDCS is considered a safe and feasible method that is easy to apply. No serious adverse effects or irreversible injuries have been reported in tDCS human trials (Antal et al., 2017; Bikson et al., 2016). The most commonly reported adverse effects are mild itching or tingling sensations. Other rare adverse effects reported are headaches, burning sensations, and discomfort. To reduce the risk of skin burns, it is important to follow safety guidelines, such as not using old or dried-out sponges and using a sufficient amount of gel or saline.

In randomized controlled trials (RCTs), one group of participants receive active tDCS, while the other receive sham tDCS (control group). Sham tDCS involves ramping up and down the current in a similar manner as active tDCS, but the target intensity is only delivered for a couple of seconds (Woods et al., 2016). In this way, the sham group will feel the same tingling sensation as the active group but will not receive sufficient doses of current to modulate neuronal activity. To increase blinding, an anesthetic cream applied over the skin areas where the electrodes are placed can reduce the skin sensation of active tDCS (Guleyupoglu et al., 2014).

2.2.2. Mechanisms of action

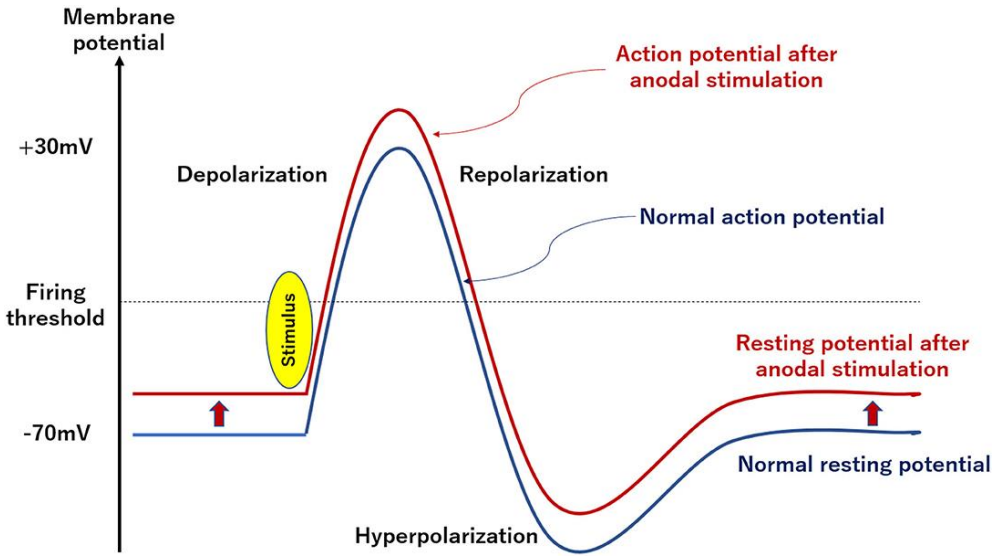
The effects of tDCS in the cortices can be divided into non-synaptic and synaptic mechanisms, which cause short-term and long-term effects, respectively.

2.2.2.1. Short-term effects

Neurons are electrically excitable cells that communicate with each other through action potentials. A certain potential threshold is needed for the resting membrane to depolarize so that an action potential can take place. The potential of the neural membrane depends on afferent activity through electrical and chemical synapses. The membrane potential can also be affected by extrasynaptic substances that activate ion channels and receptors. tDCS modulates the resting membrane potential to become either more depolarized or hyperpolarized (Nitsche & Paulus, 2000) (Figure 2). If the current results in a depolarization of the resting-state membrane, less afferent activity is needed to induce an action potential. In contrast, if the current hyperpolarizes the resting membrane potential, a stronger afferent activity is needed for an action potential to occur (Stagg et al., 2018). Modulation of the resting membrane potential can be seen as an acute effect of tDCS, lasting up to one hour after stimulation. However, if the technique is going to be of clinical importance, patients also need to experience longer-lasting cognitive enhancement that can benefit their daily lives.

Figure 2

TDCS effect on resting membrane potential



Note. Figure from Yamada and Sumiyoshi (2021), with permission to reuse.

2.2.2.2. Long-term effects

The longer-term effects of tDCS are characterized as synaptic aftereffects, with mechanisms that are consistent with use-dependent synaptic plasticity, known as long-term potentiation (Liebetanz et al., 2002; Nitsche & Paulus, 2000). The synaptic aftereffects can be categorized into NMDA receptor-dependent aftereffects and those affecting the gamma-aminobutyric acid (GABA)-ergic interneurons and glutamatergic synapses (Hansen, 2012). The similarity to long-term potentiation (LTP) is supported by studies showing how excitability changes are prevented when NMDA receptors are blocked. NMDA receptor agonists, on the other hand, enhance anodal tDCS (Nitsche et al., 2003). Studies using magnetic resonance spectroscopy (MRS), measuring regional brain metabolites, show a decrease in GABA and an increase in glutamate after anodal stimulation (Kim et al., 2014; Stagg et al., 2009). Both GABA and glutamate, being inhibitory and excitatory neurotransmitters, are crucial mediators of LTP. Both increased cortical excitability and LTP are considered crucial mechanisms for the improved cognitive effects on different neurodegenerative diseases in tDCS studies (Pellicciari & Miniussi, 2018).

2.2.3. TDCS to treat symptoms of AD

The idea that tDCS can be used to "normalize" brain functions in patients with AD is intriguing. TDCS has been proposed as a potential treatment for AD based on the idea that it can modulate brain activity and improve cognitive function. TDCS increases cortical excitability, promoting neuronal depolarization, which is altered in AD. It can also increase the level of acetylcholine in the brain, a neurotransmitter that is important for memory and learning. A reduction in the levels of acetylcholine in the AD brain has been associated with memory loss and other cognitive deficits. Reduced plasticity is also observed in the AD brain, and by using tDCS, plasticity may be facilitated, leading to increased cortical activity and better conditions for learning.

The first tDCS studies on AD patients showed optimistic results (Boggio et al., 2012; Boggio et al., 2009; Ferrucci et al., 2008). Patients improved significantly on visual and verbal recognition memory tasks after tDCS treatment. In the following decade, the results were more mixed. Several studies showed an improvement in cognitive function for the patient group receiving tDCS (Im et al., 2019; Khedr et al., 2014; Khedr et al., 2019). Other RCTs did not show statistically significant results in favor of active tDCS versus sham tDCS (Bystad et al., 2016; Cotelli et al., 2014). Case reports from both Bystad et al. (2017) and Penolazzi et al. (2015) noted improvement in global cognition after tDCS treatment. A meta-analysis by Cai et al. (2019), based on seven studies with a total of 146 AD patients, concluded that tDCS had a significant effect on improving cognitive function overall. However, the results must be interpreted with caution due to the great heterogeneity between studies. An overview of clinical studies using tDCS to treat AD can be found in Table 1.

Table 1

Clinical trials on tDCS and Alzheimer's Disease

Authors et al.	Design	Electrode position		cm2	Outcome
		Anode	Cathode		
Gangemi (2020)	RCT	l FTL	r FL	25	↑ cognitive tests & EEG
Liu (2020)	Cross-over	r&l TL/FL	Inion	35	↑ cognitive tests
Khedr (2019)	RCT	r&l TP	l dm	35	↑ cognitive tests
Im (2019)	RCT	l DLPFC	r DLPFC	36	↑ cognitive tests
Bystad (2017)	Case	l TL	r FP2	35	↑ cognitive tests
Andrade (2016)	Case	l DLPFC	sup OA	35	↑ cognitive tests
Bystad (2016a)	RCT	l TL	r FL	35	No ↑ cognitive tests
Bystad (2016b)	Case	l TL	rFL	35	↑ memory
Penolazzi (2014)	Case	l DLPFC	r sup OA	A: 35 C: 100	Stable cognitive tests
Suemoto (2014)	RCT	l DLPFC	r O	35	No ↑ apathy
Khedr (2014)	RCT	l&r DLPFC	cont. sup OA	A: 24 C: 100	↑cognitive tests
Cotelli (2014)	RCT	l DLPFC	r dm	A: 25 C: 60	No ↑ memory
Boggio (2012)	Cross-over	TL	r dm	A: 35 C: 64	↑ memory
Boggio (2009)	Cross-over	l TL, l DLPFC	r sup OA	35	↑ memory
Ferrucci (2008)	Cross-over	r&l TL	r dm	A: 25 C: 64	↑ memory

Note. RCT: randomized controlled trial, r: right, l: left, TL: temporal lobe, FL: frontal lobe, ↑: improvement, DLPFC: Dorsolateral prefrontal cortex, TP: temporoparietal region, dm: deltoid muscle, O: orbital, sup OA: superior orbital area, cont.: contralateral.

Among tDCS studies on patients with AD, most either stimulate the left medial temporal lobe or the left DLPFC with anode stimulation. The rationale behind stimulating the medial temporal lobe is to reach the hippocampus and surrounding structures that are essential for memory. In AD, these structures are the first to be affected by neurodegeneration. The rationale behind stimulating the DLPFC is its importance for many higher cognitive functions and the increased activation in these areas when AD patients perform memory tasks, compared to younger adults (Grady et al., 2003; Pariente et al., 2005). The majority of reviews and meta-analyses on the topic conclude that tDCS in AD patients is promising, but due to the great variability in patient selection, placement of electrodes, duration and

frequency of tDCS stimulation, and different outcome measures, it is challenging to derive a conclusion on clinical efficacy (Chang et al., 2018; Lefaucheur et al., 2017; Liu et al., 2017; Majdi et al., 2022). The tDCS parameters and their impact on treatment success need to be further investigated to find the optimal treatment practice.

2.2.3.1. Generalizability and transferability from tDCS protocols applied on other populations to Alzheimer's patients

With the advantages of tDCS, it is important to explore the possibilities of using the technique as a treatment option, especially for conditions offering limited options to patients (Bikson et al., 2016). Most tDCS studies using human subjects are based on young, often student, populations (Habich et al., 2020). Consequently, tDCS protocols are mostly based on this particular population. As the brain grows older, cognitive function declines as a consequence of structural and functional alterations in the brain. Age-related changes need to be considered when choosing stimulation protocols. Protocols not adjusted for this population may partly be the reason why tDCS results are heterogeneous. Habich et al. (2020) demonstrated anatomical variations between young and old adults. In neurodegenerative patients, such as AD patients, these structural and functional brain differences are even more prominent. There are significant differences in gray matter volume, white matter damage, network-related volume loss, and hippocampal volume loss in the AD brain compared to the healthy aging brain (Fjell & Walhovd, 2010; Thompson et al., 2004).

2.2.4. Adjustable tDCS parameters

The range of tDCS parameters that can be adjusted makes it difficult to compare studies and draw conclusions about the optimal stimulation procedure. TDCS methods are constantly refined. However, one advantage of the huge variety of stimulation parameters is the possibility to individualize and optimize treatment.

Defining transcranial electric stimulation involves all parameters of the stimulation device that affect the current flow generated in the brain (Peterchev et al., 2012). A range of different stimulation parameters can be manipulated on the tDCS device, in addition to between- and within-subject factors (Bikson et al., 2012; Thair et al., 2017; Woods et al., 2016) (Table 2).

Table 2

Sources contributing to the variability among tDCS studies

On the tDCS device	Procedural	Between subjects	Within subjects
Electrode montage: number, size, shape and position	Online/ offline design (Task during tDCS)	Anatomical properties: head size, skull- and skin thickness, hair volume, CSF values, gray-and white matter.	Brain state: Alertness, anxiety, motivation, attention
Session duration	Interval between sessions		Intake of neuroaffective substances (e.x. nicotine)
Amplitude of the current	Total number of sessions	Neurotransmitter levels (especially GABA)	

The adjustable parameters that this thesis focus on are 1) the EF distribution across different electrode montages, 2) the importance of anatomical properties, and 3) the total number of tDCS sessions.

2.2.5. Computational modeling to study the tDCS-induced EF

Modern technology makes it possible to track the tDCS-induced current and calculate the intensity and density across different brain regions. MRI-derived computational modeling is based on MRI scans segmenting the head into different tissues: skin, skull, gray matter, dura, and CSF (Datta et al., 2009). Computational modeling predicts the current flow generated in the brain for a specific stimulation configuration. The path of the current depends on anatomical features, current intensity, and electrode positions. The electric current will choose the path of least resistance. Tissues with low resistance are the skin, gray and white matter, and especially CSF. The skull, on the other hand, has a high resistance, causing a substantial part of the current to be shunted in the skin and passed to the cathode electrode without entering the skull or brain tissue. A study by Miranda et al. (2013) showed that a significant proportion of the applied current is shunted away from the brain, with the fraction depending on factors such as electrode size and spacing, tissue conductivity, and current intensity.

The specific individual anatomy of the gyri and sulci, the amount and distribution of CSF, and the thickness of the scalp and skull affect the pathway of the EF. Truong et al. (2013) demonstrated how inter-individual variability in anatomy between participants affects the tDCS current. They evaluated a range of bipolar and HD-tDCS montages in MRI scans of obese and low body mass index humans. Antonenko et al. (2021) studied how the EF varies

between younger and older adults, concluding that the variations come from many factors, including atrophy, head anatomy, and brain state. Older adults had higher inter-individual variability in the spatial distribution of the EF compared to younger adults (Antonenko et al., 2018). Supporting the role of CSF as a super highway for the current, Mahdavi and Towhidkhah (2018) demonstrated that aging participants with gray matter reduction and higher CSF levels had lower current intensities in brain regions underneath the electrodes than younger participants without atrophy. While bipolar montages have been proven to give widespread distribution, HD-tDCS produces more focalized EF over the target region (Bikson et al., 2012; Csifcsák et al., 2018; Datta et al., 2009).

The AD brain differs significantly from a healthy older brain regarding structural alterations of gray and white matter and disputed connectivity in networks. There is also great variability in the amount of atrophy between AD patients with similar cognitive impairments. Variation in brain anatomy influences the EF in the brain, warranting the need for individualized head models (Datta et al., 2009; Indahlastari et al., 2020). This thesis aimed at further exploring how these anatomical properties affect EF distribution.

2.2.6. Home-based tDCS

Studies show that repeated tDCS sessions might increase the duration of tDCS effects on behavioral outcomes (Boggio et al., 2007). Multiple visits to a research lab can be a burden for both patients and their caregivers, and AD patients can be difficult to recruit for clinical trials (Clement et al., 2019; Grill & Karlawish, 2010). A study by Valiengo et al. (2013) reported that the burden of regular visits was listed as the main reason why participants dropped out of multiple session-tDCS clinical trials. TDCS equipment is inexpensive compared to other non-invasive brain stimulation techniques. The apparatus is also portable, which makes treatment at home possible.

Two clinical studies have performed home-based tDCS treatment for patients with AD. An RCT by Im et al. (2019) showed that anodal stimulation over the left DLPFC improved scores on the Mini Mental Status Examination (MMSE) and Boston Naming Task compared to the sham group. They also reported stable glucose levels in the active group receiving stimulation, while a decrease was reported for the sham group. The active group received daily sessions of 30 minutes of stimulation over six months. A case study by Bystad et al. (2017) reported an AD patient receiving eight months of daily 30-minute anodal stimulation

over the temporal lobe. The results showed that immediate recall improved by 39% and delayed recall improved by 23%, in addition to preserving general cognitive functions.

A clinical guideline for remotely supervised tDCS for clinical trials reported that, in order to keep home-based tDCS safe and well-tolerated, follow-up visits from the researcher are important to ensure the correct use of the tDCS device (Charvet et al., 2015). In addition, hands-on training and prefixed electrodes are important to increase correct placement and make devices easier to use (Hagenacker et al., 2014). Other more specific considerations for the AD patient group are whether they are able to correctly monitor the tDCS device by themselves. Adverse effects in this patient population are of extra concern due to thinner skin in older adults, which may be a risk factor for skin burns.

3. General Research Questions

The main objectives of this thesis were to investigate the effect of tDCS on improving memory impairment in AD patients. This work was aimed at supplementing existing knowledge on the possible advantages of offering brain stimulation to AD patients suffering from memory impairment by exploring how different stimulation parameters affect the success of tDCS treatment. In Paper I and Paper II, the parameter "tDCS electrode position" was studied. Paper I was conducted as an RCT study, where HD-tDCS was used to target the DLPFC. Computational modeling was used to increase the precision of the stimulated target region for each patient. For further analysis of the tDCS-induced current in AD patients and healthy matched controls, a computational modeling study was conducted in Paper II based on MRI scans collected from a freely available database. In Paper III, the stimulation parameter "repetition frequency" was explored by offering home-based daily tDCS to AD patients over a four-month period. Paper I combine computational modeling and behavioral data, while Paper II is based exclusively on computational data and Paper III solely on behavioral data.

The main research questions were as follows:

1) How does HD-tDCS over the DLPFC affect performance on delayed memory when each patient's electrode montage is optimized to have the highest net sum of anodal current in the target region?
2) How does variation in brain anatomy influence current distribution in AD patients compared to healthy controls, considering both bipolar tDCS montages and HD-tDCS montages?
3) What effect do daily doses of tDCS have on cognitive functions in patients with AD, and is the procedure tolerable and feasible?

4. Methods

4.1. Overview of study design

Table 3

Overview of study design

Papers	Data	Design	Outcome measures
Paper I	Patients with AD (N = 19)	Pilot Study RCT design	RBANS, MMSE-NR3, Clock Drawing Test, TMT A, tDCS-induced EF, MRI
Paper II	MRI of AD and healthy (N = 48)	Computational modeling study	tDCS-induced EF, MRI
Paper III	Patients with AD (N = 8)	Patient series	RBANS, MMSE-NR3, Clock Drawing Test, TMT A, Adverse effects, Feasibility

4.2. Participants

The patients with AD who participated in Papers I and III were recruited from the Hospital of Northern Norway in Tromsø. To be included in the studies, participants had to meet the criteria for the diagnosis of probable AD, according to the National Institute of Neurological and Communicative Disorders and Stroke Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984; McKhann et al., 2011), specifically section 4.2: "Probable Alzheimer's disease with increased level of certainty." Participants were required to be between 60 and 85 years old and have a MMSE score of <17, and if medicated for AD, their dose should have been stable for at least three months. Exclusion criteria included psychiatric diagnoses or severe sight and/or hearing disabilities that could affect cognitive testing. In addition, patients with MRI-interfering metal in their bodies were not eligible to participate in Paper I.

In Paper I, 19 participants (14 females) were randomly assigned to receive either active HD-tDCS (N = 10) or sham HD-tDCS (N = 9). The participants were between 61 and 83 years old, with a mean age of 72.58 years. The mean MMSE score at the pretest was 21.26.

In Paper II, the data was based upon 48 MRI scans collected from the Oasis 3 study in the freely available database XNAT (Herrick et al., 2016). Of the 48 participants (17 females), 24 of the MRI scans were from patients diagnosed with AD, while 24 were from healthy matched controls. The mean age was 72.05 in the AD group and 70.36 in the control group.

The mean MMSE score differed significantly between the two groups, with a mean of 17.04 in the AD group and 29.71 in the control group.

In Paper III, eight participants (four females) received active bipolar tDCS. The participants had previously been enrolled in the RCT study (Paper I), with a minimum of a four-month pause between the two studies. The participants were between 65 and 81 years old, with a mean age of 75 years. The mean MMSE pretest score was 23.3.

4.3. Transcranial direct current stimulation

In Paper I, HD-tDCS was applied to the DLPFC using a Starstim® tDCS system from Neuroelectrics. The montage consisted of five round-shaped electrodes (⌀12 mm), with one anode electrode in the middle (2 mA) surrounded by four cathode electrodes (0.5 mA each). The montage was optimized for each participant based on the results from computational modeling (see "Electric field distribution"). The electrodes were fixed to the head using the Starstim cap for the F3 montage and a 128-channel EEG cap for the other montage. For the HD-tDCS group, the current was ramped up to 2 mA over a duration of 30 seconds and remained at this strength for 19 minutes before it was ramped down to 0 mA over the last 30 seconds. The tDCS was delivered with an accelerated tDCS design with 20 minutes of HD-tDCS: 15 minutes of rest, 20 minutes of HD-tDCS, 15 minutes of rest, and 20 minutes of HD-tDCS a day. This design was repeated over two days, with a total of six HD-tDCS sessions. According to the instructions on the Starstim device, gel was applied to the electrodes, both to increase conductivity and to reduce skin irritations. In addition, a local anesthetic cream was applied to all participants 30 minutes prior to stimulation to both reduce discomfort in the active group and increase blinding between the active and sham groups.

In Paper II, tDCS-induced current from both bipolar and HD-tDCS montages was simulated with computational modeling using the freely available software SimNIBS (see "Electric field distribution"). Electrode sizes and positions were based on previous clinical studies applying tDCS over the DLPFC. In addition to the individualized HD-tDCS montage used in Paper I, we included a "standard F3 montage" according to the 10–20 EEG system.

In Paper III, a bipolar montage was applied with a Sooma tDCS stimulator. This machine is designed for home use, focusing on its ease of use and prefixed stimulation settings. Anodal tDCS with an intensity of 2 mA was applied over the left temporal lobe (T7 according to the 10–20 EEG system), while the cathode electrode was placed over the right DLPFC (F4 according to 10–20 EEG). The electrodes were saline-soaked and round-shaped (⌀4.5 cm).

Each session lasted for 30 minutes and was administered once a day for four months. When pressing the start button, the current was ramped up to 2 mA during the first 30 seconds, remained at this intensity for 29 minutes, and was then ramped down to 0 for the last 30 seconds.

4.4. Outcome measures

4.4.1. Cognitive testing

In the two clinical trials (Papers I and III), participants underwent a cognitive test battery before and after tDCS stimulation. Immediate- and delayed-memory tests from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) were the primary cognitive outcome measures. Secondary outcome measures included the rest of the RBANS battery, MMSE, Clock Drawing Task, and Trail Making Test (TMT)-A.

4.4.1.1. RBANS

All participants in Papers I and III completed the Norwegian version of the RBANS (Randolph et al., 1998). RBANS is a standardized neuropsychological test battery used in both basic research and clinical assessment of patients with AD (Duff et al., 2008; Garcia et al., 2008; Randolph et al., 1998; Schmitt et al., 2016). The battery covers five age-corrected indexes: i) immediate memory, ii) verbal function, iii) visuospatial function, iv) attention, and v) delayed memory, with a total of 10 different tasks. Each index has a mean score of 100 and a standard deviation of 15, in addition to a total scale/full score. The test takes 30–40 minutes to complete. The immediate memory index consists of a 10-item list that is repeated four times, and the participant is asked to immediately recall the words. In addition, a story is repeated two times, and the participant is to immediately recall the story. The delayed memory index consists of both verbal and visual memory tasks. After approximately 20 minutes, the 10-item list is used to test recall and recognition, whereas the story is used to test recall. In addition, there is a visual recall test of a complex figure. Reliability coefficients are between 0.81 and 0.94 for the population between 60 and 89 years (Randolph et al., 1998). The test shows high specificity (82%) and sensitivity (98%) for the detection of AD and good test-retest reliability (Duff et al., 2008). The Norwegian version of RBANS applies Scandinavian norms (Randolph, 2013). It is based on the U.S. version (Randolph et al., 1998) and has two alternative forms (A and B) to reduce possible practice effects. In Papers I and II, version A was administered as a pretest and version B as a posttest. In Paper III, version A was used for posttest two.

4.4.1.2. MMSE

MMSE (Folstein et al., 1975) is one of the most widely used cognitive screening tools worldwide to detect and measure cognitive impairment, both in clinical trials and in general practice (Lezak et al., 2004). MMSE is easy to use and quick to administer, and hence, quite popularity. It covers seven domains: i) orientation, ii) immediate memory, iii) attention, iv) recall, v) language, vi) practical skills, and vii) copying. The test has shown good test-retest reliability, sensitivity, and specificity for detecting dementia (Tombaugh & McIntyre, 1992). However, the screening toll is less sensitive for detecting early stages of dementia, and scores are affected by age, education level, and socioeconomic status (Crum et al., 1993; Matthews et al., 2012; Nelson et al., 1986). The limitations have led to many revised editions. In the present studies, a revised Norwegian version of MMSE-NR3 was used.

4.4.1.3. The Clock Drawing Test

The Clock Drawing Test (Freedman et al., 1994) is a commonly used screening tool for dementia, especially AD (Aprahamian et al., 2009). It is administered both to detect and to follow up on cognitive impairment, giving information about several cognitive skills that are affected in the early stages of AD, such as short-term memory, understanding of verbal instructions, spatial orientation, abstract thinking, planning, concentration, and executive and visuospatial skills. The task involves asking the person to draw a clock face, including all the numbers and hands indicating a specific time.

4.4.1.4. Trail Making Test

The TMT is a widely used test in neuropsychology. It was originally developed in 1944 as a part of the Army Individual Test Battery and consists of different versions, with the most common versions being TMT-A and TMT-B (Crowe, 1998). The TMT provides information about attention, visual search, scanning, speed of processing, mental flexibility, and executive functioning (Tombaugh, 2004). The goal is to complete the tests as accurately and as quickly as possible. TMT-A requires participants to connect a series of circles numbered 1 to 25 in order. TMT-B, which involves connecting circles that alternate between numbers and letters in an ascending order, was too challenging for the AD patients. Thus, only TMT-A was administered as a part of the cognitive battery.

4.4.2. MRI data analysis

In both Papers I and II, MRI scans were analyzed for volume, surface area, and thickness using T1 and T2 weighted images. FreeSurfer, a freely available software for MRI analysis,

was used with version 6.0 software and the recon-all processing pipeline (Fischl, 2012). The segmentation outputs were visually inspected in FreeView for severe errors such as skull strip errors, segmentation errors, and pial surface misplacement. No severe errors were detected, and no manual corrections were needed.

In Paper I, the analysis of cortical thickness and surface area was performed using Permutation Analysis of Linear Models (PALM) within the FreeSurfer software package. White matter tracts were automatically reconstructed with TRActs Constrained by UnderLying Anatomy (TRACULA) to analyze tracts connecting the medial temporal lobe to the frontal lobes or pathways near the stimulated region, including the left anterior thalamic radiation (lATR), left cingulum cingular bundle (lCCG), and forceps minor (FMIN).

In Paper II, volume, cortical thickness, and area were collected from the output of the Ranta atlas based on FreeSurfer data (Ranta et al., 2014; Ranta et al., 2009). The Ranta atlas is an automated MRI parcellation of the frontal lobe in FreeSurfer that divides the frontal lobe into 10 regions in each hemisphere. The region of special interest in Paper II was the DLPFC.

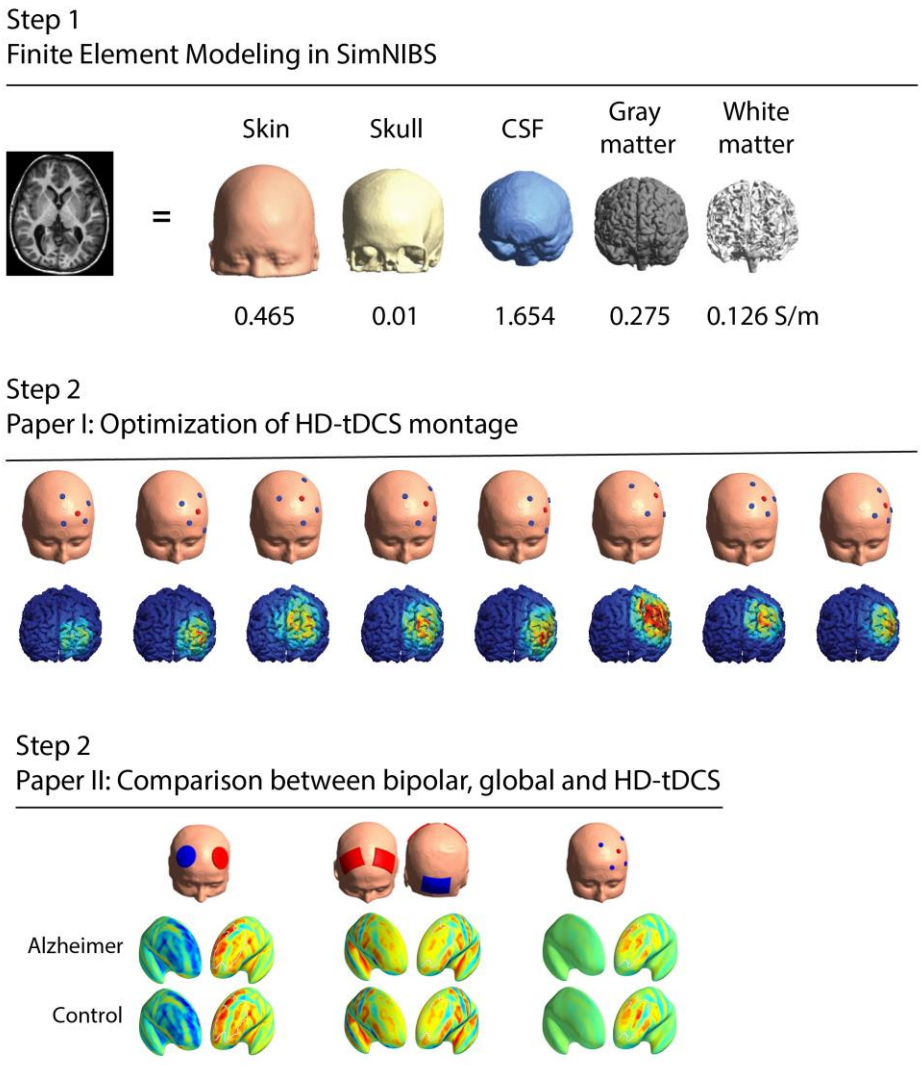
4.4.3. Electric field distribution

For both Papers I and II, the calculations of the tDCS-induced EF were run in SimNIBS, version 2.1, a freely available software for computational modeling of non-invasive brain stimulation (www.simnibs.org/) (Thielscher et al., 2015). SimNIBS uses finite element methods (FEM) to calculate the EF distribution in individual head models based on anatomical MRI data. FEM divides the human head into thousands of small elements, and the EF distribution within each element is estimated by solving equations that describe the flow of current through that element. The overall EF distribution in the head is then obtained by combining the solutions for all of the individual elements (Saturnino et al., 2015). Connectivity values are assigned to each tissue (skin, skull, CSF, gray matter, and white matter) by SimNIBS. The FEM models give information about current flow based on tDCS intensity, resistivity of the different head tissues, head anatomy, and electrode parameters. In Paper I, SimNIBS was used to find the HD-tDCS montage over the left DLPFC with the strongest anodal current strength, while, in Paper II, SimNIBS was used to compare tDCS montages used in previous AD studies (Figure 4). In Paper II, the tDCS-induced EF was quantified based on the normfield and normal component values across the whole brain and on peak 1% hotspots in the DLPFC. The normfield measures the intensity of the EF, including both current entering (anodal effects) and leaving the brain (cathodal effects). The

normfield is defined as the ratio of the desired target field strength to the actual field strength produced by the electrodes. The normal component differentiates between the current entering or leaving the cortex and is used to estimate the strength of the stimulation at each point in the brain tissue. The hotspots were used as a focality index, with hotspots referring to the location on the scalp where the EF produced by the tDCS electrodes is the highest or where the current density is most concentrated. In the modeling study (Paper II), positive and negative hotspots in the DLPFC were reported.

Figure 4

Workflow of computational modeling in Papers I and II



4.5. Statistical analysis

To test whether HD-tDCS had an effect in Paper I, comparing active treatment with sham treatment, generalized linear models (GLM) were used. The change scores (baseline: posttest) of the variables in the RBANS battery, MMS, TMT, and Clock Drawing Test were used as dependent variables in separate analyses. Group baseline performance of the dependent variable, sex, and age of the participants were included as factors and covariates. No random or repeated effects were included to keep the model as simple as possible due to the small sample size. A GLM was chosen to reduce the possibility of violating the assumption of normally distributed residuals in ordinary linear regression.

In Paper II, the computational modeling study, a Bayesian approach, was chosen to compare tDCS-induced electric fields across both different montages and between Alzheimer's patients and controls. Bayesian regression is a statistical method for modeling the relationship between a dependent variable and one or more independent variables. The analysis involves prior knowledge about the parameters of the model and allows for uncertainty about these parameters to be expressed in the form of probability distributions. A numerical estimate is calculated, in search of "the best model" (hypothesis), to explain the data. Bayesian regression models can be used to estimate the EF distribution in the brain based on individual differences and other experimental factors—in this case, current intensity and electrode placement. In that way, we could estimate how much factors such as group difference (AD versus healthy controls), electrode montages, and degree of atrophy affected the tDCS-induced field.

In Paper III, the home-based tDCS study, change scores were calculated in a similar manner as in Paper I, comparing the baseline score with test scores after treatment. Paired samples t-tests were used to determine if the mean change score was significantly different from zero. The Friedman test, which is a non-parametric statistical test, was used for the variables that were non-normally distributed.

4.6. Ethics

The two clinical studies, Papers I and III, were approved by the Regional Committee for Research Ethics in Medicine and Health Science (Paper I: 2017/794, Paper III: 2018/1662) and were conducted in accordance with the Declaration of Helsinki. Both the patient and their caregiver had to sign an informed consent form. Information about the study was given both verbally and in written form. Clinicians made an evaluation of each patient to determine if they could consent to participate. All information was stored and published anonymously.

Several ethical challenges arise when conducting clinical trials on vulnerable elderly people with AD (Chandra et al., 2021). Compared to cognitively intact individuals, AD patients need more intense follow-up and higher caregiver involvement (Korczyn, 2007). In addition to cognitive impairment, elderly people with AD may have physical impairments and a lower threshold for burden compared to young, healthy participants. Neuropsychological testing, in addition to completing the MRI session needed in Paper I, could be considered a burden for some AD participants. In order to make participation as gentle as possible, we limited the neuropsychological test battery to a manageable amount based on clinical experience. Caregivers were allowed to be present, and we helped with any logistics, as necessary. In the home-based study, we provided close monitoring with both home visits and telephone follow-up calls. Due to ethical concerns, we decided not to include a control group in the home-based study, considering that the study required participant involvement daily over a four-month period.

5. Summary of research papers

5.1. Paper I

Rasmussen, I. D., Boayue, N. M., Mittner, M., Bystad, M., Grønli, O. K., Vangberg, T. R., Csifcsák, G., & Aslaksen, P. M. (2021). High-Definition Transcranial Direct Current Stimulation Improves Delayed Memory in Alzheimer's Disease Patients: A Pilot Study Using Computational Modeling to Optimize Electrode Position. *J Alzheimers Dis*, 83(2), 753-769. https://doi.org/10.3233/jad-210378.

The aim of this study was to investigate the effect of HD-tDCS on memory performance in patients with AD by increasing neuronal excitability in the left DLPFC using tailored electrode placement determined by individualized computational modeling. A total of 19 patients were randomly assigned to receive either active HD-tDCS over the left DLPFC or sham HD-tDCS in a double-blind fashion. Cognitive tests were administered before the first HD-tDCS session and two days after the last session, and structural MRI data and DTI data were analyzed.

Computational modeling was used to analyze eight different montages over the DLPFC for each subject to determine the montage producing the maximal anodal tDCS-induced field in the DLPFC. Of the eight possible montages, four were chosen as optimal for at least one patient, with most patients having the classical F3 montage as the montage that gave the maximal anodal tDCS EF in the left DLPFC.

The main findings showed that the active HD-tDCS group had significant improvements in delayed memory and the MMSE-NR score compared to the sham group. There was also a significant positive correlation between FA in the HD-tDCS group in the anterior thalamic radiation and the score change on delayed memory. However, no significant correlation was found between structural MRI data and the tDCS effect. There was a non-significant positive correlation between the net sum of current delivered to the left DLPFC and the effect of tDCS on the cognitive scores, indicating that individuals who received more current to these brain regions had a larger effect of tDCS.

5.2. Paper II

Rasmussen, I. D., Mittner, M., Boayue, N. M., Csifcsák, G., & Aslaksen, P. M. (2023). Tracking the current in the Alzheimer's brain - Systematic differences between patients and healthy controls in the electric field induced by tDCS. *Neuroimage: Reports*, 3(2), 100172. https://doi.org/https://doi.org/10.1016/j.ynirp.2023.100172.

The objective of Paper II was to investigate the distribution of tDCS-induced EF in AD patients and healthy controls. The study used computational modeling to simulate both bipolar and HD-tDCS montages over the DLPFC used in previous clinical studies. In addition, an extra HD-tDCS montage over the F3 was included to compare an individualized computational-based electrode placement to a scalp-based electrode placement.

The data was collected from the Oasis 3 study in the XNAT database, which included MRI scans from 24 AD patients and 24 matched controls. We used FEM to calculate the EF for each MRI scan.

The main finding of the study was that the AD patients had a thinner cortex, reduced cortical volume, and higher levels of CSF compared to the healthy controls. These structural differences had an effect on the tDCS-induced EF, with weaker EF observed in all montages for the AD group and higher variability of EF distribution in the AD group compared to the healthy controls.

The simulation revealed variations in EF distribution between bipolar and HD-tDCS montages for both groups. While the bipolar montages produced a widespread EF, the HD-tDCS montages provided focal stimulation over the left DLPFC. The individualized and F3 HD-tDCS montages produced comparable EF with only minor differences.

5.3. Paper III

Grønli, O. K., Daae Rasmussen, I., Aslaksen, P. M., & Bystad, M. (2022). A four-month home-based tDCS study on patients with Alzheimer's disease. *Neurocase*, 28(3), 276-282. https://doi.org/10.1080/13554794.2022.2100710.

The aim of this patient series was to investigate the feasibility and tolerability of daily, home-based bipolar tDCS stimulation in patients with AD, as well as the potential effect of this treatment on cognitive function. Eight AD patients were given 30-minute daily sessions of anodal stimulation over the left temporal lobe for four months, with a stimulation intensity of 2 mA. The cathodal electrode was placed above the supraorbital cortex. Practical training was provided to the participants and their caregivers at the hospital, and follow-up visits were conducted at home and via telephone. Cognitive tests were performed at baseline, post-treatment, and four months after the treatment ended.

Although there were no statistically significant differences in cognitive test scores after tDCS treatment, there was a trend of either improvement or stabilization of test scores after four months of the treatment, followed by a decline in cognitive performance after four months without treatment. Only a tingling sensation was reported as a side effect, and the daily tDCS sessions were deemed tolerable and feasible for the AD patients.

6. Discussion

The aim of this thesis was to explore some of the sources contributing to the great variability of treatment success in tDCS studies on AD patients. More specifically, the parameters of electrode montage, individual factors of brain anatomy, and stimulation frequency were studied using an RCT study, a modeling study, and a patient case series.

6.1. Summary of main findings

6.1.1. Delayed memory improved after active HD-tDCS

Delayed memory was significantly improved in the AD group that received active HD-tDCS as compared to the sham group, including both visual and verbal memory. MMSE scores were also significantly improved in the group receiving active HD-tDCS. The discovery of enhanced performance following tDCS is consistent with previous findings in some clinical trials, where anodal tDCS was given to AD patients over the left DLPFC (Boggio et al., 2012; Im et al., 2019; Khedr et al., 2014). However, studies by Suemoto et al. (2014) and Cotelli et al. (2014), both which also stimulated the left DLPFC with an anode electrode, did not find active tDCS to be favorable over sham tDCS.

Despite mixed results, a newly published meta-analysis concluded that stimulation over the left DLPC is the most effective protocol for AD patients (Šimko et al., 2022). All previous tDCS studies on AD patients have used bipolar tDCS. Considering our findings in Paper II with different EF distributions in bipolar and HD-tDCS montages, it is challenging to compare the results from bipolar tDCS studies with those of our HD-tDCS study. Therefore, Paper I should be seen as a proof-of-principle study showing promising results for offering HD-tDCS over the left DLPFC to AD patients.

6.1.2. MRI data and its implication for tDCS treatment

In this thesis, MRI data were utilized to predict tDCS-induced EF in each AD brain and to explore the relationship between cognitive outcome measures following tDCS and structural MRI data (such as volume, thickness, and area) and DTI measures (such as FA and MD in white matter tracts).

In this paper, we applied computational modeling to optimize electrode montages to achieve maximum anodal stimulation in the DLPFC for each participant. This procedure was based on previous findings that atrophy and increased levels of CSF in patients with MCI can affect the EF distribution (Mahdavi & Towhidkhah, 2018). When calculating the maximal anodal

current strength across eight different DLPFC montages, four of the montages were chosen for at least one participant, indicating that tDCS-induced EF was influenced by anatomical differences. For most participants, the classical F3 montage was the preferred montage.

In Paper II, we further investigated the effect of variations in brain anatomy using additional MRI scans, including both AD brains and healthy aging adults. Here, we found that the optimized HD-tDCS montage used in Paper I and the standard HD-tDCS montage using F3 for locating the left DLPFC caused slightly different EF distributions. However, the distribution differences were so small that they are unlikely to be of clinical significance. The major influence on EF distribution was whether the montage was HD or bipolar, causing focal and widespread EF, respectively. Our findings suggest that focalizing the current using HD-tDCS rather than individually optimizing electrode montage based on anatomy is more important when the goal is to reduce interindividual differences in EF

Previous computational modeling studies have shown that bipolar tDCS montages stimulate areas outside the region of interest (Datta et al., 2009; Laakso et al., 2016; Miranda et al., 2013; Saturnino et al., 2015). Our results in Paper II are in line with these findings and contribute to the understanding of the EF distribution in an AD-affected brain. However, comparing previous tDCS trials on patients with AD can be challenging due to the heterogeneity in methodology (da Silva et al., 2022). Our computational modeling compared only previous studies with DLPFC montages and did not consider montages centered over other brain regions, such as the medial temporal cortex.

Our findings in Paper II showed that different montages created variations in the EF distribution. This is consistent with the study by Woods et al. (2016), which demonstrated that a 1 cm movement in electrode position changed the distribution and intensity of the predicted current flow in the brain. Laakso et al. (2016) compared electrode montages over the motor cortex with different montages over the frontal cortex. They found that the EF was easier to control in the motor cortex by adjusting the location of the electrodes, while moving electrodes over the frontal cortices maintained variability in the EF distribution. Using the focalized HD-tDCS reduces the influence of electrode placement, making it easier to compare studies using the same 10–20 EEG navigation, although there are individual differences in brain anatomy.

6.1.2.1. Increased tDCS effect associated with preserved gray and white matter

In Paper I, we did not find a statistically significant relationship between structural MRI data (volume and cortical thickness) and improvements in delayed memory after tDCS treatment. However, there was a tendency toward a positive correlation between cortical thickness and score changes in delayed memory. This tendency may imply that patients with more preserved gray matter benefit more from tDCS treatment than patients with greater atrophy. Our results from the DTI analysis support this theory, as we found a statistically significant positive correlation between FA values in the anterior thalamic radiation and the change score on delayed memory. The anterior thalamic radiation links the thalamus to the DLPFC (Niida et al., 2018), and patients with better-preserved white matter connections between the stimulation site and the thalamus/hippocampus benefitted the most from HD-tDCS. If this bundle is only moderately damaged, communication between the anterior thalamus/hippocampus and the left DLPFC may be enhanced by increasing DLPFC excitability. It is important to note that the sample size is small, and therefore, the results should be interpreted with caution. Despite this, the results are considered interesting and can be further explored in larger trials with a sufficient number of participants.

Individualizing tDCS parameters based on individual characteristics may enhance the effectiveness of stimulation (Hunold et al., 2023). In our HD-tDCS study, delayed memory significantly improved compared to sham HD-tDCS stimulation. Suen et al. (2021) retrospectively showed that participants with higher EF strength had better behavioral outcomes after tDCS sessions, while Antonenko et al. (2021) demonstrated that younger participants with higher EF strength had a more favorable tDCS outcome than older participants. Our findings in Paper II, which suggest that AD brains and healthy matched controls have different EF, suggest the need for separate guidelines for the dosage, electrode placement, and additional parameters when delivering tDCS to AD patients. In addition, Indahlastari et al. (2020) used computational modeling to demonstrate that current density did not correlate with chronological age but with the degree of atrophy, suggesting that the degree of atrophy may need to be considered when determining the appropriate current dose in healthy older adults. Overall, individualizing tDCS parameters and considering individual characteristics may enhance the effectiveness of tDCS.

The association between preserved white and gray matter, EF strength, and delayed memory in our findings supports the recommendation for delivering tDCS in the early stages of the disease. With the literature showing increased plasticity in the early stages of the disease, the AD brain may be more susceptible to neuroenhancement. Supporting this statement, a review by Cai et al. (2019) concluded that tDCS may be beneficial in the mild and moderate stages of the disease.

6.1.2.2. Bipolar montages may cause unwanted inhibitory fields

In Paper II, we investigated the distribution of EF across different DLPFC montages. The majority of the montages were bipolar, with the anode electrode over the left DLPFC, while the cathode electrode was placed over the right DLPFC. Bipolar montages cause upregulation of one region of the brain (under the anode electrode) while downregulating another (under the cathode electrode) (Reinhart et al., 2017). While the anode electrode is typically the focus of tDCS studies seeking to increase neuronal activity, the current density underneath the cathode electrode also affects the brain (de Berker et al., 2013). In some cases, the inhibitory effects under the cathode electrode may be desirable, depending on the clinical application and the targeted brain region. For example, inhibiting the right DLPFC while increasing activity in the left DLPFC may help reduce depressive symptoms in individuals with depression.

In excitatory tDCS studies, the cathode electrode is often placed in the bilateral hemisphere. All the bipolar tDCS studies included in Paper II had this setup, except for Im et al. (2019) who used two anodal electrodes (left and right DLPFC), placing the cathode electrode over the ion. The Im-montage caused widespread EF across both frontal lobes toward the inion. In the bipolar montages, the EF was also widespread, although with an anodal effect in the left DLPFC and a cathodal effect in the right DLPFC, causing an inhibitory force in the right DLPFC. The right DLPFC is involved in a variety of cognitive processes, including attention, working memory, and executive function, and the effects of inhibiting the right DLPFC in AD patients are not well-established. Inhibiting the right DLPFC with a cathode electrode could have unintended negative effects on cognitive functions in AD patients. In AD, activation in bilateral frontal areas is understood as a compensatory mechanism rather than an inappropriate hyperactivation. Downregulating the right DLPFC may, therefore, inhibit activity that is important for executing memory tasks effectively and is important to consider when interpreting results.

In Paper III, a bipolar montage was used, with the anode electrode placed over the left medial temporal lobe and a cathode electrode over the right DLPFC. However, this montage may have influenced the cognitive outcome measures, as the right DLPFC was inhibited under the cathode electrode. Unfortunately, at the time of enrolment, no HD-tDCS devices were suitable for home-based treatment. Applying the apparatus and obtaining sufficient contact with all electrodes (low impedance) is more challenging with HD-tDCS than with bipolar tDCS. In the future, HD-tDCS should be made more feasible so that it can be included in home-based studies. Moreover, HD-tDCS may be able to target deeper brain regions that are difficult to reach with bipolar tDCS due to the limited penetration depth of the current.

6.1.3. tDCS is a feasible home-based intervention

The findings in Paper III indicate that self-administered tDCS using a home-based kit was feasible and well-tolerated by the patient group, with no significant side effects reported except for a mild tingling sensation. However, there were no significant changes in cognitive test scores after treatment, despite slightly higher mean scores on almost all measures. The small sample size of the study may have limited statistical power, and a larger sample size may have revealed significant effects. Based on the results from Papers I and II, HD-tDCS would have been preferred if a home-based device was available, as it allows for more precise control of the current. Moreover, an "online design" in which patients undergo cognitive tasks while receiving tDCS could have improved treatment effect. However, the use of cognitive training in combination with non-invasive brain stimulation is controversial and has been associated with negative effects in tDCS studies on MCI and AD patients (Chu et al., 2021). This finding warrants the need for special guidelines when delivering tDCS to AD patients.

One important ethical consideration in conducting research involving populations with limited life expectancy is balancing the potential clinical benefits of a treatment with the time and effort required to administer it. While including a control group would have improved the quality of the home-based tDCS study, the ethical considerations of administering sham stimulation for an extended period of time to AD patients cannot be ignored. It is also important to consider the progressive nature of AD when interpreting the results of clinical studies lasting several months. Studies have found an average annual decline of 2.5 to 3 points on the MMSE score in AD patients (Lopez et al., 2009; Sabbagh et al., 2019), indicating that a stable score over time may also indicate treatment success. Future studies could increase the number of daily tDCS sessions and extend the duration of home-based

studies beyond four months, as previous research has shown positive results on cognition with eight months of daily tDCS sessions at home (Bystad et al., 2017).

6.2. Limitations

6.2.1. Limitation of sample size

The major limitation of both clinical trials (Papers I and III) is their small sample size. The problem of a small number of participants in clinical tDCS trials is a concern in the tDCS field in general (Horvath et al., 2014; Thair et al., 2017) and is highly applicable in Alzheimer studies, where few clinical trials have over 30 participants. Low participation in RCT studies and other clinical trials is a key challenge when conducting Alzheimer's research (Clement et al., 2019; Grill & Karlawish, 2010). Low sample sizes are also affected by the late diagnosis of patients with AD (Clement et al., 2019; Watson et al., 2014). Patients with AD often require a study partner to accompany them to the lab, which can be a barrier to participation if the study is conducted during the day. In the RCT study, efforts were made to be flexible with the study timing, but too many variations can again affect the validity of the study. In the home study, participants only had to visit the hospital three times during the eight-month period. Another challenge we faced here was that the participants had to live with someone who could help them administer the daily use of the tDCS device. Some patients were excluded since they lived alone at home, raising ethical questions concerning what patients can be offered this treatment in the future. Potential solutions include the use of home services to administer therapy to those living alone.

Small sample sizes in clinical trials can lead to both Type I and Type II errors, resulting in inaccurate or unreliable findings. Type I errors occur when significant differences are detected but are not actually present in the population, while Type II errors occur when real tDCS treatment effects are missed due to inadequate sample size (Thair et al., 2017; Woods et al., 2016). Matching participants based on relevant characteristics such as age, cognitive profile, and sex can improve the accuracy of results, but this can be challenging in small sample sizes and affect the randomization procedure. In Paper III, a sham tDCS group was not included due to ethical considerations of administering a sham treatment over several months to patients with a progressive disease.

6.2.2. Limitation of outcome measures

6.2.2.1. Limitations of cognitive tests

Cognitive tests serve as indirect measures of the effect tDCS may have on cognitive functions. These tests can be influenced by factors such as brain state and alertness. Patients with AD may experience variations in memory performance, reporting both good and bad days. Therefore, RCT studies with an adequate number of participants are necessary to account for these variations in brain state. In Papers I and III, RBANS was utilized to measure memory functions, including immediate memory, delayed recall, and recognition. Although RBANS has been standardized for individuals aged 20–89 years and is commonly used in research and clinical practice, it is not commonly used as an outcome measure in tDCS research. The index "delayed memory" in RBANS does not differentiate between verbal and visual memory. Other tests, such as the California Verbal Learning Test, can be employed to examine more specialized aspects of memory. RBANS was chosen due to its comprehensive assessment of a range of cognitive abilities in combination with its quick and easy administration, which is particularly useful for patients who may tire easily or struggle to focus for longer periods. It is considered to have high validity and reliability (Duff et al., 2008) and has the ability to monitor progression and treatment effects due to alternative versions. When testing participants repeatedly, a learning effect may occur, but this effect has been shown to be reduced for AD patients due to their memory impairments. Other methods for measuring memory, such as self-reported measures, behavioral measures, and brain imaging techniques, are available and should be considered in future studies to increase ecological validity.

6.2.2.2. Limitations of computational modeling

The MRI-derived computational modeling used in this thesis is a theoretical model that predicts where the electric current flows. However, the tDCS current is also influenced by other factors besides brain anatomy, such as brain state and cell orientation, which cannot be measured using structural MRI (Stagg et al., 2018). Nevertheless, studies that combine neurophysiological data and computational modeling have shown an association between the predicted EF and decreased GABA levels (Antonenko et al., 2019). The methodology of current flow modeling has been verified in surgical patients and other studies, which support computational models as a reliable and meaningful approach when studying the tDCS-induced electric current in the brain (Hunold et al., 2023; Opitz et al., 2016).

6.2.3. Reliability and validity concerns

High reliability indicates that the same results can be achieved using the same methods under the same circumstances. To increase reliability in our clinical studies and reduce the influence of external factors, we chose to keep the circumstances as consistent as possible. The cognitive tests were administered in a specific manner, and a procedure protocol was developed so that each researcher followed the same steps. Stimulation duration was fixed on the tDCS device, and participants were given the same information and tested in the same location.

In Paper I, all testing and administration of HD-tDCS were done at the university, and the study was double-blinded. However, some participants chose to read during stimulation, some rested, and others participated in conversations, either with the researcher or with their caregivers. This variation in activity may have caused differences in individual brain states. If the participants had engaged in a task during tDCS, this could have increased reliability since the circumstances during tDCS would have been more consistent.

In Paper III, stimulation sessions were conducted in the homes of the participants, which meant there was less control over the conditions, such as the timing of the sessions and the activities that participants engaged in during stimulation. However, all information about the study, training in the use of the tDCS device, and cognitive testing was provided at the hospital by the same researchers, increasing the reliability of the study.

To evaluate the validity of the cause-and-effect relationship of whether tDCS improves cognition in AD, both internal validity (the design of the experiment) and external validity (the generalizability of the results) must be considered. The design in Paper I was a double-blinded RCT, increasing the internal validity of the study. However, the two groups differed statistically in terms of age and baseline memory score, which could threaten the internal validity of the study. Nevertheless, the statistical analysis with GLM takes these factors into account, making it possible to conclude that the active group had a significantly higher change score despite these differences. In the home-based study, there was no control group, which increases the possible influence of confounding variables.

External validity is addressed if the results can be generalized to the whole AD population. If selection and exclusion criteria are too strict, external validity can be threatened (Rothwell, 2006). In our clinical studies, the patients had to be able to provide informed consent. This leads to the exclusion of patients at more severe stages of the disease. Several AD patients

have additional diseases (Franklin, 2015), and excluding comorbidity threatens the external validity. In our inclusion criteria, we did not differentiate between early and late onsets of the disease or other subgroups of AD. In general, the classification of neurodegenerative disorders is getting more and more complex due to the possibilities of studying different biomarkers (Jack et al., 2010). AD is considered a complex disease, making it extra challenging to find one common cure. By individualizing the tDCS procedure, we have highlighted the importance of using AD patients when creating guidelines for this population, instead of relying on study protocols based on healthy, younger participants. Although clinical studies may be challenging to conduct, they are important to increase external validity.

6.3. Future directions

Computational modeling enables the estimation of current intensity, direction, and distribution in the brain. Our modeling study shows that individuals with AD have lower levels of EF reaching the cortex, which is likely due to atrophy and increased levels of CSF. To increase the therapeutic effect of tDCS, computational modeling can be used to first predict the current intensity in each brain and then adjust the intensity on the tDCS device to ensure that patients receive the same amount of EF in the cortices. Indahlastari et al. (2020) proposed upregulating the tDCS dose in older adults to compensate for the effect of atrophy on EF. Reckow et al. (2018) showed that an HD-tDCS intensity of 3 mA is indeed tolerable in healthy older adults. However, more research is needed to determine whether the AD population can tolerate the same dosage as older adults. As Mahdavi and Towhidkhah (2018) stated, brain atrophy in the AD brain causes a different current pattern, which is supported by the results in Paper II. Due to increased CSF matter, the current is less controlled, and unintended areas may receive stimulation.

Another possibility for optimizing treatment is to adjust the electrode placement according to the cognitive profile of each patient (Cruz Gonzalez et al., 2018). For example, AD patients with depressive symptoms may benefit from tailored electrode montages placed to best reach underlying cortical structures associated with both their unique cognitive impairments and psychiatric symptoms. In addition, regulating intensity in response to the degree of atrophy can also be optimized in the same study and could be investigated in future research.

The variation in brain state during stimulation can lead to mixed results in tDCS studies (Woods et al., 2016). Using an online design can make the brain states of patients more

similar. Moreover, the rationale behind online designs is to probe the stimulated areas with task-relevant exercises, where tDCS can facilitate these processes by lowering the threshold for neuronal firing.

In addition to MRI data and computational modeling, other modern technologies are also valuable in understanding the underlying mechanisms of tDCS. Human studies have used PET, EEG, and MRS to trace GABA and glutamate levels to demonstrate tDCS effects. For instance, a study by Marceglia et al. (2016) used both cognitive tests and EEG as outcome measures to examine the effect of tDCS on AD patients. They reported that the abnormal EEG pattern typically observed in AD patients was partially reversed after anodal tDCS, supporting modulation of cortical activity. Another study by Im et al. (2019) explored the cerebral glucose metabolism after six months of daily tDCS using FDG-PET. The results showed that glucose levels were preserved in the active group, while they decreased in the sham group. Furthermore, MRS can be used to measure glutamate and GABA levels, which provides an important interpretation of the outcomes of tDCS in the brain since LTP depends on the modulation of these neurotransmitters (Heimrath et al., 2020). In the future, it is important to integrate these modern technologies into clinical research to further understand the impact of tDCS on the AD brain and its potential to modulate disrupted brain activity. However, tDCS for use in AD is still considered experimental, and further research is needed to fully understand its effects and determine its clinical efficacy.

7. Overall conclusion

HD-tDCS over the left DLPFC improved both delayed memory and global cognition in AD patients. The results support the potential of offering HD-tDCS to AD patients. Computational modeling revealed that inter-individual differences in brain atrophy among the patients resulted in different electrode montages when opting for the highest net sum of anodal stimulation in the left DLPFC. Patients with better-preserved white matter connections had the highest change scores, indicating that tDCS treatment may be more effective in the early stages of the disease.

AD-related pathology caused a weaker and more widespread tDCS-induced EF in the brain compared to healthy matched controls. The anatomical variations between AD and healthy adults must be considered when creating stimulation protocols. To reduce the effects of inter-individual brain anatomy, HD-tDCS montages can be used instead of bipolar montages. For focalizing, the current HD-tDCS is recommended over bipolar montages.

Home-based bipolar tDCS was found to be both feasible and tolerable for AD patients. No significant cognitive improvement was found. A major limitation in both clinical trials is the low sample size. Despite promising results, additional studies with larger sample sizes are needed to draw a conclusion on the effect of HD-tDCS in AD patients. In the future, additional neurophysiological measurements should be added to increase our understanding of the underlying effects of tDCS treatment.

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Paper I-III

Paper I

High-Definition Transcranial Direct Current Stimulation Improves Delayed Memory in Alzheimer's Disease Patients: A Pilot Study Using Computational Modeling to Optimize Electrode Position

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Paper II

Tracking the current in the Alzheimer's brain - Systematic differences between patients and healthy controls in the electric field induced by tDCS

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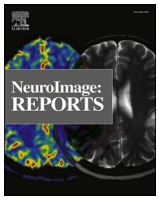

Tracking the current in the Alzheimer's brain - Systematic differences between patients and healthy controls in the electric field induced by tDCS

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ABSTRACT

Background: Several studies on patients with Alzheimer's disease (AD) have used transcranial direct current stimulation (tDCS) to enhance neural excitability in the left dorsolateral prefrontal cortex (lDLPFC). Interindividual differences in brain anatomy in AD patients pose a challenge to efficiently target the lDLPFC using scalp-based coordinates, calling for new and more precise tDCS protocols.
Objective: The purpose of this study was to explore how AD-related neuropathology affects the tDCS-induced electric field (EF) across different DLPFC montages using computational modeling.
Method: Forty-eight realistic head models were created from structural magnetic resonance scans of AD patients and healthy controls collected from a publicly available database. We compared the tDCS-induced EF in different montages applied in the literature, in addition to a high definition (HD)-tDCS montage centered at electrode F3.
Results: There was an overall global reduction in EF strength in the patient group, probably due to structural alterations that were also identified in the patient group. A widespread distribution of the EF was found across the frontal lobe for bipolar montages, while HD-tDCS yielded more focal stimulation, mainly restricted to the lDLPFC. Minor differences in the EF distribution were found when comparing the HD-tDCS montages.
Conclusion: Neurodegenerative alterations present in patients with AD affect the magnitude, distribution and variability of the EF. HD-tDCS montages provide more focal stimulation of the target area, compared to bipolar montages with to pronounced group differences between AD patients and healthy matched controls. This finding poses substantial limitations to the comparison of cognitive effects of tDCS both between patients and controls and within patients at different stages of disease progression.

In Alzheimer's disease (AD), neural activity is severely affected by neurodegenerative processes (Frisoni et al., 2010). By applying electric current to brain regions associated with memory performance, several studies have aimed to facilitate neural connections and enhance memory function for these patients using transcranial direct current stimulation (tDCS) (Cai et al., 2019; Chang et al., 2018).

The first tDCS studies on AD patients reported optimistic results, showing that tDCS improved patients' performance on recognition memory tasks (Boggio et al., 2009, 2012; Ferrucci et al., 2008). However, the following decade yielded rather mixed results (Bystad et al., 2016; Cotelli et al., 2014) challenging the therapeutic potential of tDCS in AD. Cappon et al. (2016) highlighted the diversity of the methodological approaches used in the field of tDCS in cognitive rehabilitation: Studies targeted different cognitive functions, with variable current intensities, electrode dimensions and stimulation durations. Clearly, the application of more standardized protocols is necessary to provide sufficient evidence for the effectiveness of this intervention, before clinical guidelines can be made (Lefaucheur et al., 2017). For the purpose of optimizing stimulation protocols, we first need to identify the main sources of variability. Here, we propose that computational modeling can help transition from incidental parameters such as electrode size and location and focus instead on the active component of the method, the intensity of the electric field (EF) in the target area.

Computational modeling enables the prediction of the magnitude and spatial distribution of tDCS-induced EF in the brain, providing crucial insights into the neural mechanisms and associated behavioral

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outcomes of this brain stimulation technique (Bikson et al., 2012; Mahdavi and Towhidkhah, 2018; Opitz et al., 2015). In addition to protocol-related factors such as electrode size, positioning and current intensity, interindividual differences in head and brain anatomy also influence the flow of tDCS-induced current (Antonenko et al., 2020; Datta et al., 2012; Laakso et al., 2016; Opitz et al., 2015).

In the AD population, there are interindividual differences in the degree of brain atrophy at different stages of the disease (Hill et al., 2011). As AD progresses, the loss of neurons and synaptic injury results in both larger ventricular areas and a reduction in gray matter (Frisoni et al., 2010). Increased cerebrospinal fluid (CSF) volume affects the current pathways (Bikson et al., 2012; Datta et al., 2012), which in turn can substantially influence tDCS outcomes in patients. Therefore, placing electrodes based on fixed coordinates on the skull does not guarantee that the target brain area receives sufficiently strong currents (Opitz et al., 2015), which indicates a need for more precise montage optimization. In addition, electrode placement in AD patients has been informed by studies on the cognitive effects of tDCS in healthy individuals. However, due to significant differences in anatomy between the AD brain and normal aging, regarding gray matter atrophy, white matter damage and hippocampal volume loss (Toepper, 2017; Vemuri and Jack, 2010; Fjell and Walhovd, 2010), both the distribution of the EF and the behavioral outcomes of tDCS can differ relative to the healthy brain. By quantifying the magnitude and spatial distribution of EF in the brains of AD patients, we can adjust the stimulation protocol to optimize cortical targeting. More precise stimulation is likely to increase the chances of treatment success (Mahdavi et al., 2014).

Bipolar montages are the most common tDCS protocols, consisting of one anode and one cathode electrode. In AD montages, the anode is often placed either above the left dorsolateral prefrontal cortex (lDLPFC) (Boggio et al., 2012; Im et al., 2019; Khedr et al., 2014; Penolazzi et al., 2015) or on the medial temporal lobe (Boggio et al., 2009; Bystad et al., 2016; Ferrucci et al., 2008), whereas the cathode is typically positioned above the right hemisphere. Bipolar montages result in approximately 50% of the induced current reaching the cortex (Nitsche et al., 2015), while the rest is shunted away. These montages are nonfocal, causing widespread currents outside the target area (Datta et al., 2012; Opitz et al., 2015), a phenomenon that can severely confound the interpretation of the cognitive or clinical effects of these protocols (Csifcsák et al., 2018).

More recently, high definition-tDCS (HD-tDCS) has been introduced (Datta et al., 2012). This stimulation protocol uses a "4 × 1 layout" consisting of an anode placed above the target area surrounded by four return electrodes (cathodes). The ring-shaped electrodes are smaller than the conventional bipolar ones, usually 1.2 cm in diameter versus the rectangular 5 × 7 cm electrodes. The 4 × 1 ring montage increases spatial focality (Alam et al., 2016; DaSilva et al., 2015). The 4 × 1 montage was used in our recently published study, where patients receiving active HD-tDCS improved significantly on delayed memory tasks compared to patients receiving sham tDCS (Rasmussen et al., 2021). Importantly, electrode positioning in this study was informed by computational modeling of the EF. However, to draw conclusions on the efficacy of HD-tDCS montages in the AD population and on the utility of individual montage optimization, a more systematic comparison between bipolar and HD-tDCS montages is needed.

In the present study, the strength and spatial distribution of tDCS-induced EF in 48 MRI-derived realistic head models were analyzed. The aim was to compare EF distributions from six different electrode montages targeting the lDLPFC and to explore the effect of anatomical variations on the EF, with special emphasis on AD-associated brain atrophy. Four bipolar montages and one HD-tDCS montage targeting the lDLPFC, which have been previously applied in the literature, were analyzed (Table 2) in addition to an standard F3 HD-tDCS montage.

We hypothesized that atrophy in the AD brains would result in more variability in the EF for all montages. Furthermore, we hypothesized that HD-tDCS would result in an EF that is more constrained to the target region than the standard bipolar positioning approach, and that the individual optimization would increase the strength of EF in the lDLPFC. Due to AD-related pathology, we also anticipated that optimized electrode placement would be more beneficial in the AD group in terms of restricting the EF to the target area. To our knowledge, there are no previous modeling studies of this nature that compared patients with diagnosed AD and healthy matched controls.

1. Methods and materials

1.1. Participants and MRI acquisition

High-resolution head models were created from T1-and T2-weighted anatomical images collected from the OASIS-3 study in the XNAT database (http://www.oasis-brains.org). The OASIS-3 is a longitudinal neuroimaging, clinical, cognitive, and biomarker dataset for normal aging and AD. Structural MRI scans of 24 AD patients (13 women; mean ± SD age: 72.05 ± 5.49) and an equal number of healthy, matched controls (14 women; mean ± SD age: 70.36 ± 2.20) were used (Table 1).

1.2. tDCS simulation

The procedure for creating the head models was semiautomatic (with manual quality-control steps) using a pipeline developed in Nipype (Gorgolewski et al., 2011). Head models were created with the "mri2mesh" routine in SimNIBS, version of 2.1 (www.simnibs.org/; Thielscher et al., 2015), a software package developed for calculating the EF induced by noninvasive brain stimulation. The "mri2mesh" routine relies on FreeSurfer (Fischl, 2012) for automatic segmentation of gray and white matter and accurate cortical surface reconstruction and FSL (Smith et al., 2004) for automatic tissue segmentation of skin, skull and CSF. Segmentation quality can be checked here: https://osf.io/9wgrq/. Calculations of the tDCS-induced EF were run using the finite element method (FEM). The FEM model gives information about the EF (both intensity and distribution) based on the tDCS dose (mA), conductance of the tissues (e.g., skin, skull, CSF, white- and gray matter), head anatomy and electrode parameters (number of electrodes, their location, shape, size, thickness, and the conductive medium: gel or saline-soaked sponge sockets). The conductivity of the head tissues was based on the default settings in SimNIBS (Supplementary Table 1).

Four bipolar tDCS montages and two HD-tDCS montages were simulated for each head model. The bipolar montages were sized and positioned as described in the original papers (Table 2), with an electrode thickness of 1 mm, circular connectors (diameter: 0.5 cm) at the middle of the electrode pads, and a sponge pocket of 2.5 mm. The current intensity was set to 2 mA for all montages. Both HD-tDCS montages were based on the extended 10/20 EEG system (Klem et al., 1999) with one anode electrode (2 mA) surrounded by four cathode electrodes (0.5 mA each), with electrodes of 1.2 cm diameter, thickness of 1 mm and a 2.5 mm gel thickness. In our "uniform" HD-tDCS montage, the anode was positioned at location F3, and the surrounding electrodes were placed at F7, C3, Fz and Fp1 in all head models. In the optimized HD-tDCS montage, the selection of the location of the anode was based on individual optimization of the magnitude of the EF in the target area

Table 1
Clinical and demographic data.

Variable	Alzheimer (N = 24)	Healthy (N = 24)	*t value*	*p value*
Sex male/female (N)	11/13	10/14	–	–
Age (M ± SD)	72.05 ± 5.49	70.36 ± 2.20	1.40	.169
Education in years (M ± SD)	14.96 ± 2.79	16.42 ± 2.67	−1.851	.071
MMSE-NR (M ± SD)	17.04 ± 4.90	29.71 ± 0.46	−12.60	<0.01*

Note. Independent T-test. M: mean, SD: standard deviation, MMSE-NR: Mini Mental Status Evaluation Revised. *Indicates $p < .05$.

Table 2
Previous DLPFC-tDCS studies on AD patients using bipolar montages.

Study	Design	Electrode position A	Electrode position C	Electrode area cm^2
Liu et al., (2020)	Cross-over	l&r DLPFC (F3&F4)	Inion (lz)	35
Im et al., 2019	RCT	l DLPFC (F3)	rDLPFC (F4)	36
Khedr et al. (2014)	RCT	l&r DLPFC	contralateral SOA	A: 24, C: 100
Boggio et al. (2009)	Cross-over	l DLPFC (F3)	r SOA	35

Note. 2 mA current intensity for all studies. RCT: randomized controlled trial, r: right, l: left.
DLPFC: dorsolateral prefrontal cortex, SOA: supraorbital area, A. anodal, C: cathodal.

(lDLPFC), derived from computational modeling. This optimization approach was recently used in our randomized pilot study involving patients with AD (Rasmussen et al., 2021). More specifically, eight different 4 × 1 montages over the DLPFC was simulated (Supplementary Figure 1 for all anode and cathode locations), where the optimal montage was chosen based on two rules. First, the highest value of the anodal current (positive values for the normal component of the EF) had to be in the lDLPFC compared to the other regions in the frontal cortex. From the montages that fulfilled this condition, the montage with the highest difference between the anodal and cathodal EF in the left DLPFC was chosen. This second rule was designed to prevent strong cathodal currents in the target area, which are associated with neural inhibition (Nitsche et al., 2003). The lDLPFC was localized using the Ranta atlas (Ranta et al., 2009, 2014), which is a parcellation of the frontal lobe into ten distinct regions in each hemisphere (see Fig. 1).

1.3. Data extraction

From the three-dimensional vector field quantifying the distribution of the EF (three-dimensional direction vectors for each of the finite-element nodes in three-dimensional space), we calculated four indices that were averaged within the brain regions:

1) The "normfield" measures the absolute strength of the EF at each node. This gives information about the EF intensity at that exact location, without taking the current direction (polarity) into account.

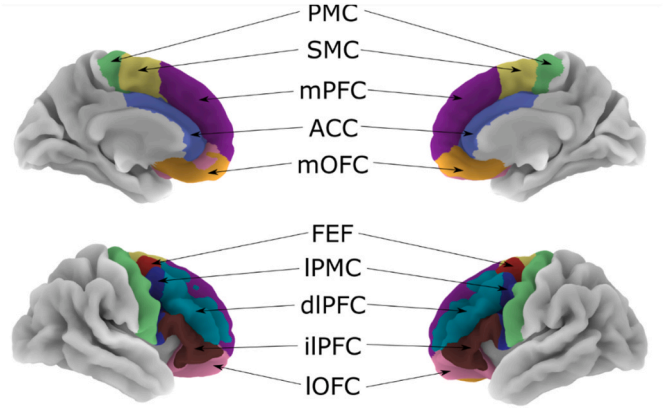

Fig. 1. The Ranta atlas dividing the frontal lobe into ten regions per hemisphere.
Note. PMC: primary motor cortex, SMC: supplementary motor complex, mPFC: medial prefrontal cortex, ACC: anterior cingulate cortex, mOFC: medial orbitofrontal cortex, FEF: frontal eye field, lPMC: lateral premotor cortex, dlPFC: dorsolateral prefrontal cortex, ilPFC: inferior lateral prefrontal cortex and lOFC: lateral orbitofrontal cortex.

2) The "normal component" reflects currents either perpendicularly entering or leaving the cortex (positive and negative values, respectively). The current entering the cortex is commonly associated with increased neural excitability ("anodal effect", positive values), whereas current leaving the gray matter toward the CSF is inhibitory in nature ("cathodal effect", negative values). For both the normfield and the normal component, region- and hemisphere-specific mean and SD values were obtained.
3) A "target focality index" for both anodal and cathodal currents, defined as the proportion of nodes in the lDLPFC with peak 1% EF intensities ("hotspots") relative to the number of hotspots in the whole cortex (Csifcsák et al., 2018).
4) The coefficient of variation in the patient and control groups to determine whether anatomical differences within groups affected the variability of the EF in the frontal lobe. The coefficient of variation was calculated as the standard deviation of the normal component divided by the mean of the normfield in each region and multiplied by 100 (Laakso et al., 2016).

We used raw EF values without any normalization.

1.4. Brain structure segmentation

The volume, area and thickness values of the MRI scans were provided by FreeSurfer version 6.0 software with the recon-all processing pipeline, including motion correction, normalization to Talairach space, intensity bias correction, skull stripping, surface registration and segmentation. FreeSurfer segmentation outputs were visually inspected in FreeView for severe errors (e.g., skull strip errors, segmentation errors and pial surface misplacement). No manual correction was performed. Values of the cortical thickness, volume and area in 10 frontal regions of each hemisphere were extracted from the Ranta atlas and compared using separate univariate ANOVA for each region (Fig. 1; Ranta, 2009, 2014). Volume measures were controlled for intracranial volume.

1.5. Analysis

To evaluate the montage- and diagnosis-specific effects (AD patients vs. healthy control subjects) on the EF magnitude and spatial distribution, we conducted sequences of hierarchical Bayesian regression models using the brms package (Bürkner, 2017). All reported analyses employ hierarchical linear models (also known as mixed-effect models) where subject-level (random-effects) and group-level (fixed effects) are combined when estimating the best-fitting model. We use Bayesian methods for estimating these models because they allow a flexible model-building process and implement advanced methods for determining effect-size estimates (using posterior means and highest-density intervals) as well as for model comparison. In all of these models, we use the EF as dependent variable (either the normal component of the EF or its non-directional intensity) and use predictor variables coding for the brain region and hemisphere (in order to account for the obvious variability in which brain regions are stimulated) as well as the montage to quantify differences between montages. Interactions between all these factors are also included in order to analyze in which region-specific montages differ from one another. Finally, and crucially, we include a factor coding for which group the participant belongs to (i.e., whether it is an AD patient or a healthy control subject). To account for inter-individual global differences in the EF (as might be caused by within-group variations of factors such as skull-thickness, for example), we added random intercepts per subject." In total, 16 models were evaluated per analysis: a null model with no predictors, four models with a single predictor, six models for all pairs of predictors and their interactions, four models for all triplets of predictor combinations and a full model with all predictors and interactions. From this ensemble of models, we selected the best-fitting model using the leave-one-out cross-validation criterion (LOOIC; Vehtari, Gelman & Gabry, 2015).

With this approach, lower LOOIC values are indicative of a better fit. All models were estimated using Hamiltonian Monte-Carlo methods (HMCs) implemented in Stan (Stan Development Team, 2016). We used four chains of 2000 samples each, where the first 1000 samples were treated as the warm-up period and discarded from the final analysis. All traces had $\hat{R}$-values below 1.05 and were visually inspected for convergence (Gelman et al., 2013). $\hat{R}$-values larger than 1.05 indicate insufficient exploration of the posterior density and would therefore prevent the interpretation of the results of the statistical model. We used the default noninformative priors implemented in brms. For all models, we report the raw regression coefficient (*b*) along with the 95% highest density interval (95% HDI), in which the true value falls with 95% probability given the validity of the model.

2. Results

2.1. Total EF-strength reduced in AD patients

The comparisons of the MRI scans showed that AD patients had a significantly thinner cortex in almost all brain regions and reduced volume compared to the healthy matched controls. In the lDLPFC the AD had a significantly thinner cortex (M = 2.26 mm, SD = 0.12) compared to the control group (M = 2.41 mm, SD(0.10), F(19.68), p < .001. For all values see Supplementary Table 2. Results of the hierarchical Bayesian regression models, testing whether this atrophy affected the total EF strength (see method section "Analysis"), showed that the model where the group effect was limited to a main effect (i.e., the effect was fixed across regions, hemispheres and montages) was preferred by the model selection (LOOIC = − 30110.3, SE = 156.1, R^2 = 0.94). The results showed that AD patients had generally reduced electric field strengths across brain regions and montages, $b = -0.011$, 95% HDI [− 0.0024, − 0.021]. For the full model-selection table, see Supplementary Table 3.

2.2. Greater EF variability in AD patients

We expected that EF distribution would show greater variability in AD patients given their greater anatomical variability. We therefore conducted an equivalent analysis of the coefficient of variation as in the previous section, where we included a main-effect-only model for the patient group in addition to the other 16 models, including the different predictor combinations. In this analysis, the winning model included all predictors, including patient group *and* all interactions between these factors (LOOIC = 34410.3, SE = 146.9, R^2 = 0.77). The second-best model was the one where patient group was included as a main effect only (LOOIC = 34416.9, Standard Error (SE) = 149.3; R^2 = 0.76) (Supplementary Figure 2 and Supplementary Table 4). In all areas and montages, the coefficient of variation was always increased in the AD group relative to the healthy controls (average increase: $b = 1.56$, 95% HDI [0.67, 2.43]). Therefore, we conclude that the variability of the EF was significantly affected by patient group and that the effect was different across montages, regions and hemispheres.

2.3. Variations in EF between bipolar- and HD-tDCS montages

To investigate the distribution of the anodal and cathodal EF, we estimated a sequence of regression models, treating the mean normal component in each brain region as the dependent variable. The best model (LOOIC = − 34257.1, SE = 193.3, R^2 = 0.94) was the full model that included all four predictors: patient group, montage, brain region and hemisphere, as well as their interactions (Supplementary Table 5). Consequently, all of these variables were predictive of the average electric field inducing anodal (positive) or cathodal (negative) currents. Fig. 2 illustrates the difference between the bipolar and HD-tDCS montages, showing both the lateral and medial aspects of the brain. Fig. 3 shows the estimated anodal and cathodal effects induced in each

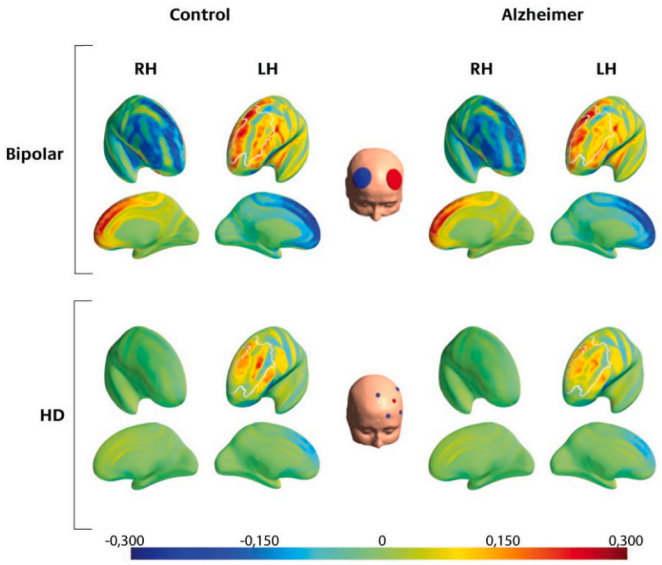

Fig. 2. Comparison of the normal component in a bipolar and an HD-tDCS montage.
Note. EF distribution for the bipolar (Im et al., 2019) and uniform HD-tDCS montage. The unit of the EF normal component is in V/m. Dark red indicates a strong inward flowing current, while dark blue represents a strong outward flowing current. For both montages, the stimulation intensity was set at 2 mA. The current in the HD-tDCS montage is more focalized, not affecting the right hemisphere. However, the anodal current in the bipolar montage is stronger.

frontal brain region in the left hemisphere separately for the two groups. Fig. 4 illustrates the spatial distribution of the anodal and cathodal effects in both hemispheres for each montage (group means and standard deviations), separately for the patient group and the healthy matched controls.

The profiles for the three bipolar montages with the anode electrode over the left DLPFC and the cathode electrode over the right DLPFC (Boggio et al., 2009; Im et al., 2019; Khedr et al., 2014) are quite similar, and all show strong cathodal stimulation of medial frontal areas (MPFC/ACC/SMC/mOFC) as well as non-prefrontal areas (Figs. 2 and 3). In contrast, the nonfocal montage used by Liu et al. (2020), with one anode electrode over each DLPFC and the cathode electrode placed over the inion, shows strong anodal stimulation of the MPFC and ACC and less stimulation in non-prefrontal areas. Finally, the optimized and F3-based HD-tDCS montages showed comparably strong EFs in the target area (left DLPFC) but largely reduced EF magnitudes in the remaining frontal structures. Group differences are most pronounced in the three bipolar montages. There does not appear to be a clear difference between healthy and AD patients when using the focalized HD-tDCS montages.

2.3.1. Limited effect of optimizing the HD-tDCS montages

Following up on these results, we conducted an analysis restricted to the HD-tDCS montages. The winning model (LOOIC = − 13349.7, SE = 140.1, R^2 = 0.87) included all factors except the patient group, indicating that diverging anatomical features between the two groups did not significantly alter the induced E-field (normal component) in the HD-tDCS montages (Supplementary Table 6). However, since "montage" was included in the winning model, the optimized and F3 versions of the HD-tDCS ring-montages induced different EF distributions. Surprisingly, the average anodal EF in the target region, the left DLPFC, was slightly reduced in the optimized montage relative to the F3 montage ($b = -0.0028$; [− 0.0052, 0.0004]), even though the 95% HDI includes zero and the effect is therefore not robust.

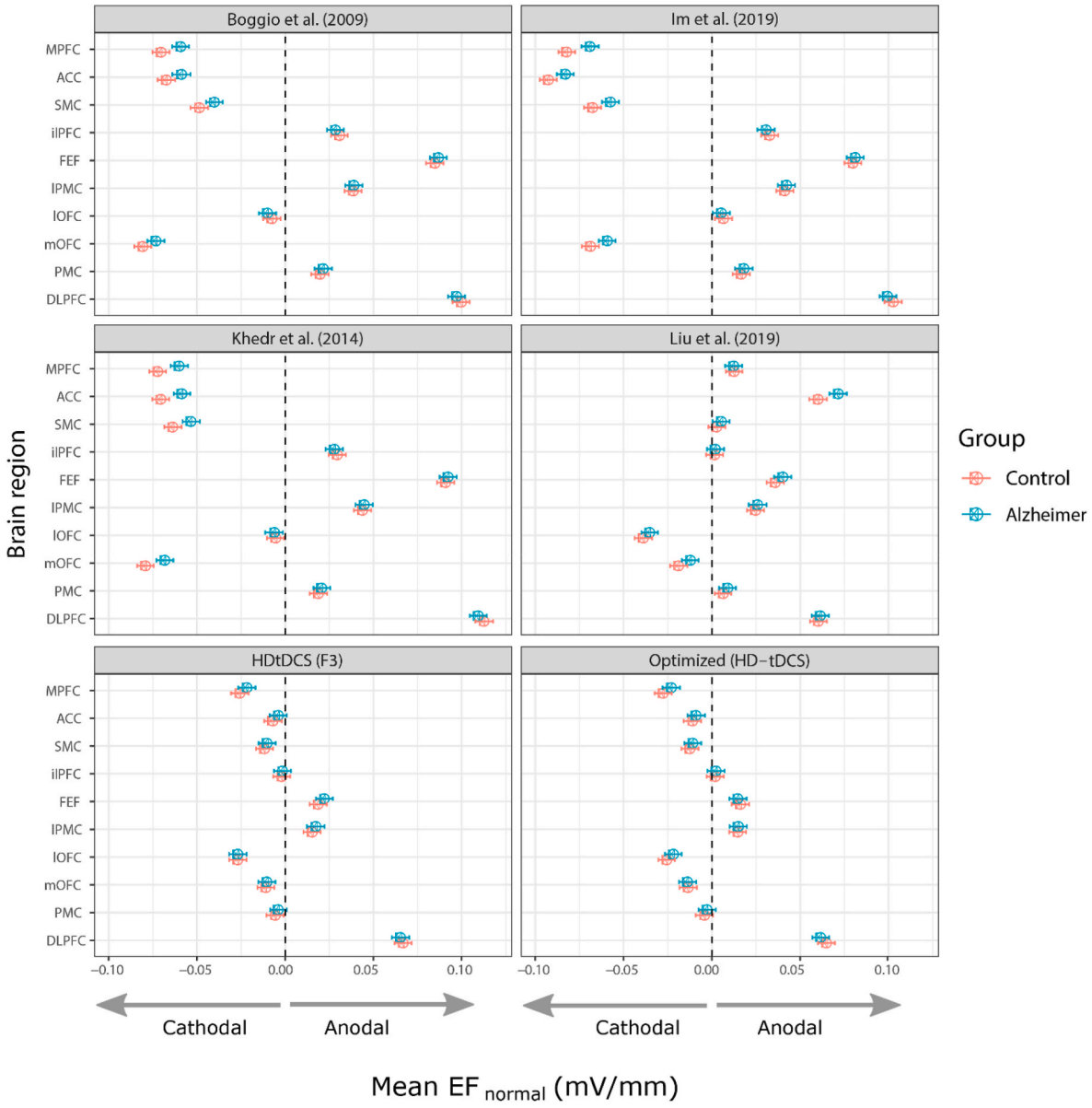

Fig. 3. Marginal means for the normal component of the electric field in the left frontal cortex for all tDCS montages.

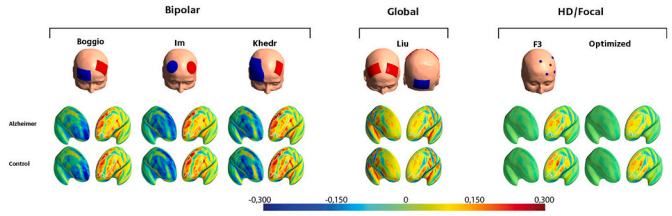

Fig. 4. Mean of the normal component across all different montages.
Note. Colorbar unit V/m. See "Table 2" for specific placements of electrodes in each montage.

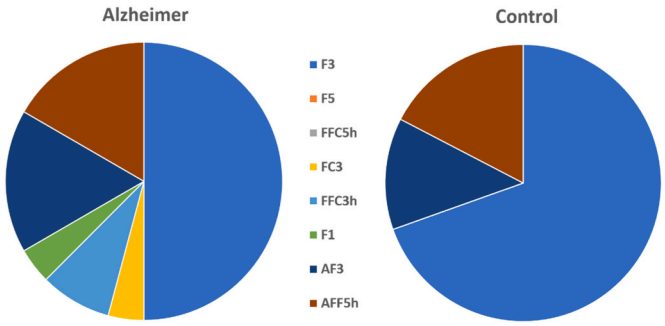

Fig. 5. Electrode montage selection for the optimized HD-tDCS protocol.
Note. Coordinates based on the 10–20 EEG system.

2.4. Selection of electrode position in the optimized montage

For the optimized montage, three different montages were chosen in the control group, while six different montages were chosen in the Alzheimer group (Fig. 5).

2.5. Focality of lDLPFC stimulation

Focality in the lDLPFC was calculated based on the percentage of nodes with the top 1% highest normal component EFs located in the

lDLPFC relative to the whole cortex. The HD-tDCS montages had the majority of high activity nodes in the target region. The three bipolar montages had approximately one-third of the high nodes in the lDLPFC, while the Liu montage had very few high-activity nodes in the target region (Fig. 6).

3. Discussion

The primary goal of the present study was to compare the tDCS-induced EF across different montages targeting the left DLPFC in AD patients and healthy matched controls using computational modeling. Anatomical comparison of the two groups showed a statistically significant thinner cortex and reduced cortical volume in the AD group. Computational modeling revealed a weaker EF strength in AD patients, in addition to greater variability across the frontal lobe in both hemispheres. The analysis showed widespread EF in the bipolar montages compared to the more focal stimulation in the HD-tDCS montages. In addition, the optimized and uniform F3 montage showed only minor differences in the EF distribution.

Our results show that the simulated tDCS-induced EF was weaker across all montages and brain regions for the AD group than for the control group, especially in brain regions not directly underneath the electrodes. These results are in line with previous modeling studies that have indicated that decreased gray matter and higher levels of CSF may reduce the current density (Laakso et al., 2016; Opitz et al., 2015). In a comparison study of three brain models (Mahdavi and Towhidkhah, 2018), an increase in CSF and gray matter atrophy was related to a reduced magnitude of current density. A study by Antonenko et al. (2020) also showed that older adults had higher interindividual anatomy, affecting the current density. Our study, with a total of 48 head models, is the first to show that the aging brain affected by AD neurodegeneration receives even less current density than the normal aging brain. Based on these results, generalization from tDCS studies on healthy adults to AD patients should only be done with great caution.

To successfully reach the brain region of interest, Habich et al. (2020) promote two conditions that need to be fulfilled. Primarily, the dose that reaches the target area in the cortex must be sufficient to modulate the cortical activity, and second, the current must reach the correct target. Since the current dose that reaches the AD brain is reduced, it is plausible that patients might benefit less from tDCS stimulation than healthy controls if the same intensity is administered. A possible solution to match the effective dose of the stimulation is to individualize the tDCS protocol based on the results from computational modeling, whereby the stimulation intensity is adjusted so that all patients receive the same EF values in the target area. Increasing current intensity from 2 mA to 3 mA would increase current density in the AD brain and is shown to be tolerable and without adverse side effects when using HD-tDCS (Reckow et al., 2018). However, as stated by both Mahdavi and Towhidkhah (2018) and Thomas et al. (2018), brain atrophy with increased CSF may lead to both “shunting” of current and congestion of CSF attracting current to brain regions outside of the target of stimulation. Another possible approach for optimizing tDCS is to regulate the duration of stimulation. Further studies are needed before concluding how these parameters influence treatment success (Lefaucheur et al., 2017).

The patient group showed higher variability in the EF distribution across the brain in all montages, especially in the bipolar montages. If the tDCS intensity is further increased in the bipolar montages to achieve higher EF values in the lDLPFC, this will also result in stronger EF in brain areas outside the target region. To ensure control over the applied current, focalized HD-tDCS montages are recommended (Alam et al., 2016; Edwards et al., 2013), with our results showing only small variations in EF intensity when using an HD-tDCS approach. Focalizing the current meets the second criteria listed by Habich for effectively reaching the target of interest (Habich et al., 2020).

Simulation of the bipolar montages showed a more diffuse EF distribution with limited focality in both hemispheres compared to the focalized HD-tDCS montages. These results are in accordance with previous findings comparing bipolar and HD-tDCS montages in nonclinical populations (Datta et al., 2012; Laakso et al., 2016; Saturnino et al., 2015). Since AD patients seem to be more dependent on both the right and left DLPFC when executing memory tasks (Grady and Craik, 2000; Pariente et al., 2005), it is important not to inhibit the right hemisphere. In the bipolar montages, the right hemisphere is cathodally stimulated, leading to an inhibitory effect on these areas. This effect was present in all bipolar montages except the Liu montage, where the right DLPFC was stimulated anodally. In depressed patients, the montage with anodal stimulation over the lDLPFC and cathodal stimulation over the rDLPFC has been proposed to be clinically beneficial because the right hemisphere is often hyperactivated in depressed patients (Grimm et al., 2007). This is not the case for AD, where activity in the right DLPFC does not necessarily indicate disrupted processing responsible for cognitive symptoms but may instead reflect a compensatory function for preserving memory (Hill et al., 2011).

Comparison of the two HD-tDCS approaches shows that there were only minor variations in the EF distribution between the optimized and the classical F3 electrode placement. Surprisingly, the classical F3 montage had slighter stronger anodal stimulation in the target area than the optimized montage. The rule for optimizing is to choose the montage where the difference between the anodal and cathodal currents in the

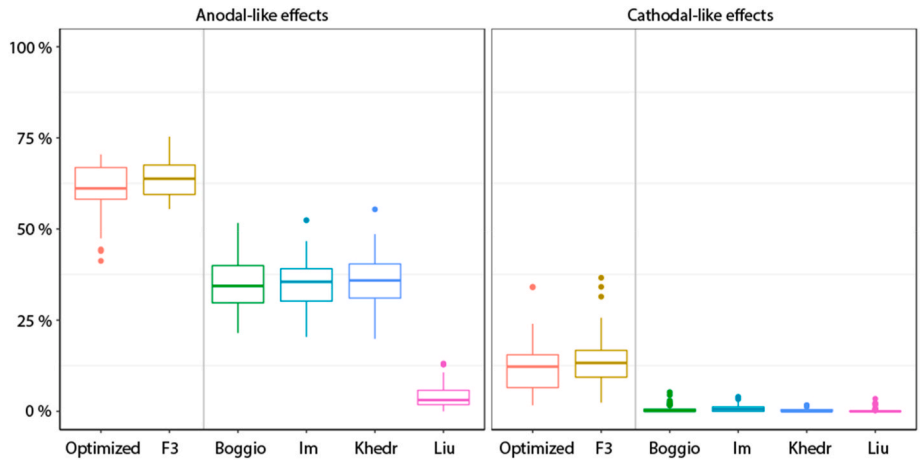

Fig. 6. Focality index of anodal and cathodal current effects in the left DLPFC. Note. Percentage of the top 1% highest normal component EFs located in the lDLPFC relative to the whole cortex.

left DLPFC was the strongest (anodal minus the cathodal current). The analysis of anodal and cathodal hot spots in the target area shows that the classical F3 montage has a slightly higher degree of cathodal hot-spots in the target area than the optimized montage. Nevertheless, the small variations present in the EF distribution are unlikely to have a strong clinical impact.

4. Conclusion

Several clinical trials have shown that tDCS can improve cognitive function in AD, but the results are not universally positive. A more detailed investigation of how the tDCS current interacts with cortical tissue in AD patients is necessary to enhance the chance of treatment success. Computational modeling simulates tDCS-induced current, calculating both the amount and distribution of EF in different brain regions, giving insight into how interindividual differences in brain anatomy affect tDCS stimulation.

Our results show that AD patients with disease-related neuropathology had reduced levels of EF and greater variability in current distribution than healthy matched controls. Bipolar montages with widespread EF across both hemispheres, were more affected by brain alterations in AD, compared to HD-tDCS montages where the EF was more focal to the target area. To reduce unwanted stimulation of nontarget brain areas, focal tDCS should be used. However, montage optimization for the HD-tDCS approach via individual, MR-based modeling seems to yield only modest benefits.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynirp.2023.100172.

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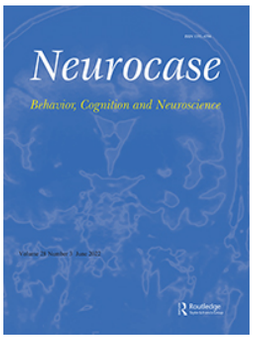
Paper III

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

Ole K. Grønli, Ingrid Daae Rasmussen, Per M. Aslaksen, Martin Bystad

Neurocase, 2022



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

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ABSTRACT

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

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

Introduction

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

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

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

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

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

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

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

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

Aims of the study

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

Methods

Participants

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

Study protocol

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

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

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

Home-based transcranial direct current stimulation

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

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

Cognitive assessment

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

A licensed psychologist conducted the cognitive testing.

Statistical analysis

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

Results

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

Table 1. Patient characteristics.

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

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Strength and limitations

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

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

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

Conclusion

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

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Authors`contributions

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

Ethical approval and consent to participate

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

Data availability statement

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

Disclosure statement

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

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