tDCS as treatment in neuro-psychiatric disorders

The underlying neuronal mechanisms of tDCS treatment of auditory verbal hallucinations

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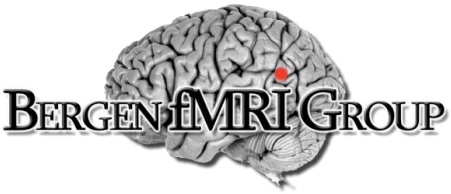
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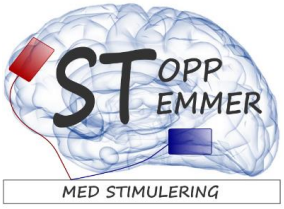
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Abstract

Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation which has gained widespread interest in neurology and psychology, both as a clinical and research tool. While it has been explored as a treatment for numerous disorders and as a potential means to improve function, there is still too little empirical evidence regarding its efficacy. So far, it is only considered effective as a treatment for depression. In schizophrenia, the tDCS montage of anodal stimulation over the dorsolateral prefrontal cortex (DLPFC) and cathodal stimulation over the temporo parietal cortex (TPC) has been proposed as treatment for auditory verbal hallucinations (AVH).

This montage is based on the hypofrontal/hypertemporal model in schizophrenia, which says that the DLPFC is *hypo*active and therefore has reduced control over the *hyper*active TPC, which causes AVH. By placing the anode over the DLPFC, which usually has an excitatory effect, activity in the DLPFC is expected to be boosted; and by placing the usually inhibitory cathode over the TPC activity is expected to be reduced. However, whether the idea that underlies the tDCS treatment is true, namely that tDCS reverses the hypertemporal/hypofrontal activity pattern, has not been studied sufficiently. In general, it is unclear what the underlying mechanisms of tDCS treatment of AVH are. Moreover, since the discovery of the tDCS treatment for AVH, the findings regarding whether it is effective have been inconsistent (Brunelin et al., 2012). Whether the hypofrontal/hypertemporal model and the hypothesized underlying mechanism of the treatment is correct has not been studied sufficiently.

Therefore, the main goal of the thesis was to study the underlying mechanisms of tDCS with multimodal neuroimaging, including functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), functional connectivity and structural imaging in both a healthy population (paper II) and a population of people with severe AVH within a randomized controlled trial (paper III). In addition, clinical measures and a behavioral task were included to examine whether the

treatment reduces AVH. To study the electric field of tDCS, simulation was performed in the specific montages of the studies.

In paper I, the opportunity arose to research, if tDCS works in a specific type of epilepsy caused by mitochondrial disease, specifically a DNA polymerase-gamma (POLG) gene mutation. A previous case study (Ng et al., 2018) raised hopes that tDCS could alleviate symptoms in such POLG patients. Paper I studied the effects of tDCS using electroencephalography and electromyography. The results showed, however, that tDCS treatment at 2mA did not lead to a statistically or clinically significant reduction of myoclonus jerking or epilepsy spikes in the 15-year old POLG patient.

In paper II, tDCS did not induce any changes in functional activity in the DLPFC or TPC and there was only a trend for higher glutamate levels (as approximated by Glx = glutamate+glutamine) in both DLPFC and TPC. Neither finding is in line with the hypertemporal/hypofrontal model. Moreover, we found that simulation of tDCS showed peak electric field strength between the electrodes (Broca's areas), not as hypothesized directly under the electrodes.

In paper III, there was a small decrease in AVH after tDCS treatment. However, this decrease only emerged in self-reports from patients but not examinations by professional clinicians and was hard to distinguish from placebo effect. None of the neuroimaging data (rs-fMRI, MRS, structural MRI nor task-related fMRI) showed significant effects for the DLPFC or TPC.

Taken together, this thesis gives an overview of tDCS treatment in neurological and psychiatric disorders based on a single case study, a healthy control population and a patient population of schizophrenia/psychosis. It was shown that tDCS does not always relieve epilepsy symptoms in POLG disease cases. With only two case studies on the subject, much more research is needed if and in which cases of POLG disease tDCS can be effective. Paper II tested the hypofrontal/hypertemporal model indirectly and paper III directly tested the notion that underlies the tDCS treatment, namely that this activity pattern could be reversed with tDCS, with multimodal neuroimaging. The results showed that tDCS reduces AVH to a certain degree. In conclusion, the findings from both paper II and III argue against the notion that the tDCS treatment

reverses the hypofrontal/hypertemporal activity pattern that is believed to underlie AVH. Our data indicated that the Broca's area should be investigated, as the peak intensity of the stimulation lies there when DLPFC and TPC are stimulated. In addition, future research should investigate the differences between tDCS responders and non-responders, preferably in a multimodal manner similar to paper II and III, as it is a crucial approach to investigate underlying neuronal mechanisms.

List of publications

I. Marquardt, L., Eichele, T., Bindoff, L. A., Olberg, H. K., Veiby, G., Eichele, H., ... & Hirnstein, M. (2019). No effect of electrical transcranial direct current stimulation adjunct treatment for epilepsia partialis continua in POLG disease. Epilepsy & Behavior Reports, 12, 100339. ISSN 2589-9864, https://doi.org/10.1016/j.ebr.2019.100339

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III. Marquardt. L., Craven, A.R., Hugdahl, K., Johnsen, E., Kroken, R.A., Kusztrits, I., Specht, K., Thomassen, A.S., Weber, S., Hirnstein, M., (2020) The underlying neural mechanisms of tDCS treatment of auditory verbal hallucinations – a multimodal neuroimaging study, *submitted* to Translational Psychiatry

The published papers, "No effect of electrical transcranial direct current stimulation adjunct treatment for epilepsia partialis continua in POLG disease" and "A multimodal study of the effects of tDCS on dorsolateral prefrontal and temporo-parietal areas during dichotic listening", are reprinted with permissions granted through open access publishing.

Table 1

Overview over the three papers included in the thesis.

	PAPER I	**PAPER II**	**PAPER III**
YEAR	2019	2020	Submitted 2020
JOURNAL	Epilepsy Behavior Reports	European Journal of Neuroscience	Translational Psychiatry
RESEARCH QUESTION?	Can tDCS relieve myoclonus symptoms or epileptic activity in POLG epilepsy?	Does tDCS change Glx levels, dichotic listening (DL) behavior or brain activation on the TPC or DLPFC?	What are the underlying neuronal mechanisms of tDCS and does the tDCS treatment of DLPFC and TPC reduce AVH hearing?
MAIN FINDINGS	No statistically or clinically significant reduction of seizures or epileptiform in the patient.	No significant differences in Glx levels, dichotic listening behavior or brain activation between real and sham tDCS.	A small reduction in AVH, but no significant imaging findings regarding tDCS in the DLPFC and TPC.
DESIGN	Case Study	Double-blind within-participant experiment	Double-blind randomized controlled study
SAMPLE	One POLG patient	32 healthy participants	21 patients with severe AVH
DATA	EEG and EMG	MR Spectroscopy, fMRI, Behavior scores, tDCS field simulation	MR Spectroscopy, fMRI and rs-fMRI, clinical and neurocognitive scores, structural MRI, tDCS field simulation
ANALYSIS	EMG and EEG spike count, analyzed with ANOVA and non-parametric Friedmann test/ paired sample t-test and non-parametric Wilcoxon tests, respectively.	rmANOVA for MRS, fMRI and DL data.	rmANOVA for most of the data.

List of abbreviations

AHCS – Auditory Hallucination Change Scale

AVH – Auditory Verbal Hallucinations

AES - Apathy Evaluation Scale

AHRS - Auditory Hallucination Rating Scale

CGI - Clinical Global Impression

DL – Dichotic Listening

DLPFC – Dorsolateral Prefrontal Cortex

EEG – Electro Encephalography

EMG – Electromyography

fMRI – functional Magnetic Resonance Imaging

GABA - γ-aminobutyric acid

GAF - Global Assessment of Functioning

Glx – glutamine + glutamate

MRI – magnetic resonance imaging

MRS – magnetic resonance spectroscopy

NART - National Adult Reading Test

PANSS - Positive and Negative Symptom Scale

POLG - DNA polymerase-gamma

rs-fMRI – resting state functional Magnetic Resonance Imaging

tDCS – transcranial direct current stimulation

TPC – Temporo Parietal Cortex

Contents

1. Introduction

1.1 Transcranical direct current stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method applied to the scalp via two or more electrodes. tDCS is often carried out in a single or multiple sessions of 10-30 minutes and, unlike transcranial magnetic stimulation (TMS), tDCS cannot in itself induce neuronal firing in the form of action potentials (Nitsche et al., 2008). It rather increases or decreases membrane potential and thereby enhances or reduces the chances of action potentials (Nitsche et al., 2008). In recent years, it has become increasingly popular as a neuroscientific research and clinical treatment tool, as it can be used to alter brain activation in the targeted areas. Its purpose can be to make the brain more efficient in some way, bring it back to earlier functioning lost due to illness, or to interfere with normal functioning to identify which brain areas are involved in a given task. The electrodes usually supply a low direct current between 0.5-2 mA, as higher currents induce painful sensations and lower currents do not have meaningful effects on brain functioning (Dubljević, Saigle, & Racine, 2014).

1.1.1 History

tDCS is a relatively new method, as it was first introduced by Nitsche and Paulus (2000) with the currently used parameters, showing that changes in excitability were induced and could last for several minutes after tDCS. The idea to stimulate the brain with electricity, however, is much older. Already the ancient Egyptians, about 2000 years ago, tried treating headache with torpedo electric fish (Sarmiento, San-Juan, & Prasath, 2016). Around the year 1800, stimulation was first used in patients with mental disorders, but due to technical shortcomings at the time it was not successful and largely abandoned. This changed by 1930 when electroconvulsive therapy was discovered, using much stronger electric currents (around 800 mA) in order to deliberately induce seizures, which is a crucial difference to tDCS, where this is avoided. Treatment with lower-electric currents was

not focused on in this time period. In the 1960s, animal studies advanced the knowledge about how low anodal currents applied directly to the cortex could increase excitability, while cathodal currents reduced it (Bindman, Lippold, & Redfearn, 1964; Creutzfeldt, Fromm, & Kapp, 1962; Purpura & McMurtry, 1965; Stagg & Nitsche, 2011). From the 1980s, human studies were done with tDCS, however their parameter settings were with very low currents under 1mA. Results were divergent, but were able to show that a small current crossing the scalp can influence the brain (Priori, Berardelli, Rona, Accornero, & Manfredi, 1998).

1.1.2 Fields of use and tDCS safety

The research on tDCS is wide, ranging from research on cognitive enhancement, for example for working memory, to its potential as treatment in a variety of mental and neurological disorders: for example, major depression disorder, stroke, aphasia, Alzheimer, Parkinson's disease, chronic pain, addiction, tinnitus and schizophrenia (Fregni et al., 2020). In science, applications of brain stimulation are to determine which brain areas are involved in a given task. Several recent meta-analyses claim that tDCS with stimulation of the left dorsolateral prefrontal cortex (DLPFC) is an effective treatment for depression (Fregni et al., 2020; Moffa et al., 2019; Mutz et al., 2019; Wang, 2019). It has also been claimed to be "probably effective" in relieving symptoms of neuropathic pain, migraine, chronic and fibromyalgia pain, improving cognitive function in Parkinson's disease, motor rehabilitation in chronic stroke, decreased seizures in epilepsy, and craving/addiction, as well as "possibly effective" in motor function in Parkinson's disease, OCD, and chronic post-stroke aphasia (Fregni et al., 2020). TMS has been classified as "definitely effective" in depression and chronic pain, and "probably effective" in motor stoke and negative symptoms of schizophrenia (Lefaucheur et al., 2014).

tDCS has a minimal side-effects profile, if safety guidelines are followed, and is usually well tolerated by participants and pain free. Typical side effects include itching and tingling or more rarely burning sensation in the area where electrodes are attached, headache and discomfort and in the worst case (very rarely and typically if

participants are predisposed to it) epileptic seizures (Brunoni et al., 2011). In order to prevent side effects, safety guidelines need to be followed. Safety measures in healthy participants include that tDCS participants should not: suffer from epilepsy or have epilepsy cases in their close family, have severe dermatitis or other open sores in the area the electrodes are attached, have any medical implants such as cochlea implants or pacemakers, should not have consumed considerable amounts of alcohol or drugs in the 24 hours prior to participation, and should not be pregnant (Antal et al., 2017). It has been established that heating of the skin and brain under tDCS electrodes is not a problem (Antal et al., 2017; Stagg & Nitsche, 2011). When treating severe disorders, for example severe epileptic seizures, the potential benefit of tDCS can outweigh the risks and the treating physician, with the consent of the patient, can decide to give tDCS despite the side effects. A key advantage of this method is that it is relatively cheap compared with other medical interventions, the cost of a tDCS machine being in the order of $10,000. Moreover, tDCS stimulators are small and hence portable, which opens up for treatment in practitioners' offices or at home after sufficient education of the proper use (Gough et al., 2020; Shaw, Pilloni, & Charvet, 2020).

1.1.3 Mechanisms of tDCS

Despite considerable advances, the underlying mechanisms of how tDCS affects the stimulated brain tissue are not fully understood. The general view is that the positively charged anode typically increases neuronal activity (i.e., it has an excitatory effect), while the negatively charged cathode typically reduces neuronal activity and, thus, has an inhibitory effect. These effects have been typically obtained with 1 mA (Nitsche & Paulus, 2000). However at 2mA, the cathode has been found to have excitatory effects (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013), challenging the view that anode/cathode are typically excitatory/inhibitory, respectively.

The amount and distribution of current on the cortex is highly affected by individual anatomical and physiological differences. Factors that affect the current

include skull thickness, the distribution of cerebrospinal fluid (CSF) and subcutaneous fat (De Berker, Bikson, & Bestmann, 2013). For example, the skull is a poor conductor and delivers little current to the underlying tissue since skull bone is the least conducting tissue in the human head. So, thick bone would mean little current, and thin bone would be preferable for tDCS. This is counterbalanced though by thicker bone often having cancellous bone which conducts well and thin skull having compact bone which does not conduct that well. Thus, both the thickness and the structure of the skull determine the amount of current that can flow from the skin to the brain (Opitz, Paulus, Will, Antunes, & Thielscher, 2015). CSF is the best conductor in the head and a thin layer increases the field strength in the underlying brain. If there is a lot of CSF, the current is carried away along the surface of the brain, instead of entering the gray matter. These factors add to the uncertainty of the strength and distribution of the delivered tDCS current.

Another important factor which determines the current flow, is the topography of the underlying cortical surface. Polarity can be reversed in adjacent sulci or gyri, and there is generally higher field strength on top of gyri and lower electrical fields with increasing depth (Miranda, Mekonnen, Salvador, & Ruffini, 2013; A. Rahman et al., 2013). The anatomy of the tissue above the brain and the topography of the brain surface itself renders the assumption that current simply flows straight inward from the electrode in an either depolarizing or excitatory manner (for anodal stimulation) too simplistic. Most of tDCS current actually flows tangentially to the brain surface (along the surface, not into the surface and deeper structures), which means that cells that are aligned parallel to the brain surface (e.g., interhemispheric connections) are more optimally stimulated than radial ones. The radial or normal component (going down into the brain from surface) of the current is strongest at the bottom of the sulci and under the electrodes, while the tangential component is practically zero directly under the electrode and spreads on the edge toward the other electrode (De Berker et al., 2013). Even within a single cell the current will have different effects, depending on the morphology of the cell. One part might be depolarized, making action

potential firing easier while other parts are hyperpolarized, making the formation of action potentials difficult.

There is an important distinction to be made between targeting a brain area with the stimulation electrode and putting an electrode "over" the brain area, because the peak of delivered current is often somewhere between two electrodes**.** To map the effects of structure on tDCS current, scientists have begun to simulate and model current intensity and distribution based on anatomical images. Here, the current flow between the electrodes is simulated based on the individual anatomy from MRI images and electrode montage in each participant (Miranda, Callejón-Leblic, Salvador, & Ruffini, 2018). It gives insight into the individual effects tDCS can have and how a specific montage influences the underlying cortex and with which intensity. It could be used to optimize individual tDCS treatment, by planning the exact position of the electrodes in the individual to give the electric field peak in the desired area. Especially between large electrodes (5x7 cm^2) that are close together, a single maximum of current will occur between the electrodes or on the edge of the electrode toward the other electrode - instead of the desired two current maxima, one under each electrode (Miranda et al., 2013). Since the electrodes are usually still placed over the area to be affected instead of behind the target area, even though the total current and the tangential component occur between the two electrodes, this could indicate that the normal current, which in fact is under the electrodes, is most important for stimulation (Miranda et al., 2013).

tDCS is often criticized for not being spatially specific enough, since the big electrodes stimulate broad brain areas. In order to increase focality in tDCS, smaller electrodes can be used. High definition tDCS uses several smaller electrodes in order to achieve this (Nikolin, Lauf, Loo, & Martin, 2019). About 50 % of the variation in the electrical field in a region of interest during tDCS can be explained from five factors I have mentioned here: 1) thickness of the skull, 2) CSF layer, 3) sulcal depth, 4) distance to the closest anode edge, and 5) distance to the cathode. Individual anatomical differences between people play a role in several of the factors (Opitz et

al., 2015). This discussion demonstrates that the simple assertion that the anode is depolarizing and the cathode is hyperpolarizing does not hold.

A study found that when stimulating the left DLPFC with anodal tDCS, perfusion increases also in the primary sensory cortex, midcingulate cortex, paracingulate cortex, and left parietal cortex compared to baseline (Stagg et al., 2013), while cathodal tDCS decreased perfusion in the thalami bilaterally and other regions. This shows that tDCS modulates regions directly under the electrode, but also in spatially distant regions that are closely related anatomically. So, when electrodes are applied to the scalp to affect a specific region below, other regions might be inadvertently activated too.

1.2 Mitochondrial disorders: POLG related epilepsy

Because of the potentially excitatory and inhibitory effects of tDCS, epilepsy was one of the early targets of tDCS treatments (Fregni et al., 2006). Epilepsy is a group of neurological disorders, characterized by epileptic seizures, which is characterized by abnormal and excessive neuronal activity and often manifests as shaking of the body or body parts and variable levels of consciousness loss (Fisher et al., 2014). tDCS has been studied as possible treatment in epilepsy (San-juan et al., 2015). A recent meta-analysis of the current evidence of cathodal tDCS treatment for epilepsy found that it is “probably effective” in decreasing seizures (Fregni et al., 2020). The patient in the first study of the present thesis suffered from mitochondrial disease, more specifically DNA polymerase-gamma (POLG) disease. POLG disease usually has an early age of onset (< 5 years) but can also occur later in life. Mitochondrial diseases have a prevalence of one in 5000 (Anagnostou, Ng, Taylor, & McFarland, 2016; S. Rahman, 2012). POLG disease is caused by a mutation in POLG – a gene that encodes mitochondrial DNA polymerase (Stumpf, Saneto, & Copeland, 2013). The mitochondrial DNA polymerase is a vital part of replicating the mitochondrial genome. Hence, when it is damaged, mitochondrial DNA is reduced. As the mitochondria are responsible for ATP production through the mitochondrial respiratory chain, damage to this system progressively disables the energy

metabolism. When the energy level in neurons falls to a critical point, it can trigger epilepsy and neuronal death. Epilepsy is common in POLG disease, estimated to be present in 50%-65% of POLG patients, with even higher probability in pediatric patients. There is a high risk for status epilepticus and therapy resistant epilepsy, and mortality is high (Bindoff & Engelsen, 2012; Hikmat, Eichele, Tzoulis, & Bindoff, 2017).

1.3 Schizophrenia and other mental disorders with AVH symptoms

Schizophrenia is a devastating mental disorder with a lifelong prevalence of around 1 % (Tandon, Keshavan, & Nasrallah, 2008). One typically differentiates between *positive* and *negative symptoms*, where positive symptoms come in addition to or are distorted from normal function while negative symptoms are characterized by a loss or decrease of normal function. Examples of negative symptoms include lack of emotions, loss of motivation, and social withdrawal. Hallucinations and delusions are examples of positive symptoms and widely regarded as core symptoms of schizophrenia. Individuals with schizophrenia further experience *cognitive symptoms* (i.e., loss of cognitive functions), such as disorganized behavior, attentional and memory deficits as well as poor decision making. The DSM V definition of schizophrenia is: two or more of the symptoms delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior and negative symptoms such as diminished emotional expression, lasting for a one-month period or longer (and at least one of them must be the first three symptoms mentioned). There has to be impairment in functioning in one or more areas of work, interpersonal relations or self-care. Some signs of the disorder must last for a period of at least six months and the disturbance must not be caused by another medical condition; in particular, schizoaffective disorder and bipolar or depressive disorder must be ruled out (American Psychiatric Association, 2013).

The disorder is very heterogeneous in its manifestation (Tandon et al., 2008), as many different symptoms are observed and patients can present very differently in

dysfunction and symptoms. Risk factors for schizophrenia are cannabis use, prenatal infection, winter birth (season of birth effect increases with severity of winter), childhood trauma, urbanity, migration and genetics (Tandon et al., 2008; Van Os, Rutten, & Poulton, 2008). Schizophrenia is heritable. If one parent has schizophrenia, the child will have a 10-20% chance of also having the disorder, if both parents have schizophrenia, the chance it is passed to their offspring increases to 40-50%. Schizophrenia has a higher prevalence in males than in females, with a 2:1 ratio. Symptom onset is typically in early adulthood 20-29 years, with women being a bit older than men on average (Rosenhan & Seligman, 1995).

Early intervention is important for disorder outcome. Not only is schizophrenia a devastating disorder for the individual and their family, but it is also highly costly for society. Mental health disorders are estimated to cost Norway 31.7 billion NOK yearly in health care expenses alone, with lost production costs coming in addition, thereby being the costliest kind of condition to the system (Kinge, Sælensminde, Dieleman, Vollset, & Norheim, 2017). With the disorder comes a heightened suicide risk, with 1% lifetime incidence of suicide in the general population, compared to 10-15% incidence amongst schizophrenia patients (Caldwell & Gottesman, 1992; Möller & Müller, 2006).

1.3.1 Auditory verbal hallucinations

As stated above, hallucinations are one of the core symptoms of schizophrenia. A hallucination is a perceived stimulus which has no real-world stimulus equivalent. Hallucinations can be experienced in all sensory modalities: perceiving smell (olfactory), touch (tactile), noise (auditory), taste (gustatory), or seeing (visual) something that is not really there. Auditory hallucinations are any kind of auditory perception without a corresponding auditory stimulus. Auditory hallucinations are the most common modality in schizophrenia patients, with 60-80% of schizophrenia patients reporting them (Andreasen & Flaum, 1991; Hugdahl, Løberg, Specht, et al., 2008; Pondé et al., 2017). They can be only noise or music, but often comprise speech or speech-like sounds. Auditory verbal hallucinations (AVH) are perceived

speech in the absence of speech stimuli. AVH manifest in several different forms: they can be clear and loud or mumbling and low in volume. Single words or short phrases are more commonly reported than long sentences. The frequency of voice hearing varies hugely from a few times a month to almost constantly, often depending on the severity of the illness and acute episodes. Some voice hearers experience having some control over the voices. However, it is much more common that voice hearers have no or little control over the voices, causing high levels of distress (Larøi et al., 2012).

Control – or more specifically, a lack thereof – is an important feature when differentiating clinical and non-clinical voice hearers, with non-clinical voice hearers experiencing higher levels of control than clinical ones (Larøi et al., 2012). There are estimated to be around 15% healthy voice hearers in the population (Beavan, Read, & Cartwright, 2011). Another factor that differentiates healthy voice hearers from voice hearers with a psychiatric diagnosis is the content of the voices, which is typically much more negative and abusive and therefore more disturbing in clinical voice hearers, often in the form of two or more voices talking negatively about the patient (Larøi et al., 2012).

1.4 Study and treatment of auditory hallucinations

AVH are inherently hard to measure and study. They are only to be measured by asking and interviewing the voice hearers who experience them. We have to trust in the description given by the voice hearer, usually patients in our studies. This is difficult, especially in patients, as they often struggle with a disturbed worldview inherent to their disorder, namely delusions. Even when patients are very cooperative and eager to share their experiences, it is often hard to understand their descriptions or it is hard for them to find the words to describe the AVH. Nevertheless, there are well established interviews and measures which give us a good indication of voice hearing severity that is scored though the combination of several individual questions, like the positive and negative symptom scale (PANSS) (Kay, Fiszbein, & Opler, 1987), the Questionnaire for Psychotic Experiences (QPE) (Rossell et al., 2019;

Sommer, Kleijer, & Hugdahl, 2018) and the auditory hallucination rating scale (AHRS) (Ralph E. Hoffman et al., 2003; Van de Willige, Jenner, & Wiersma, 1996).

Psychosis and auditory hallucinations are commonly treated with a group of medications called antipsychotics or neuroleptics. Pharmacotherapy is tailored to the individual on a trial and error basis. Antipsychotics are grouped into 1st generation or typical antipsychotics and 2nd generation or atypical antipsychotics. Among the typical antipsychotics we find: Chlorpromazin (1st antipsychotic produced), Haloperidol, Fluphenazine, Prochlorperazine and Benperidol. Examples for atypical antipsychotics are: Clozapin (1st atypical produced), Ziprasidone, Risperidone, Olanzapine and Aripiprazol (Benkert et al., 2013). The pharmacological mechanism behind antipsychotics is the decrease of dopaminergic hyperactivity in psychosis through blocking dopaminergic receptors. There are five dopamine receptors, $D_{1\text{-}5}$. Most important to the antipsychotic effect is the inhibition of the D2-receptor, which all antipsychotics do to a larger (typical) or smaller (atypical) degree (Möller & Müller, 2006). Antipsychotics affect the three important dopaminergic systems; the nigrostriatal system, which controls motorics and therefore causes extrapyramidal side effects as tremor; the mesolimbic/mesocortical system, whose up- and down-regulation causes delusions and negative symptoms and therefore is the main reason for antipsychotic effects of medication; and the tuberinfundibular system, where antipsychotics cause an increase in prolactin. In addition to dopamine receptors, serotonin and noradrenalin receptors are blocked by antipsychotics, which also influences the therapeutic effect and causes side effects. Atypical antipsychotics are usually preferred due to less extrapyramidal (movement-related) side effects. Atypicals should also have a good antipsychotic effect, usually work better against negative symptoms than typicals and have low prolactin increase (Benkert et al., 2013).

Antipsychotics have a large side effects profile caused by D2-receptor blockage in the different dopaminergic neuron-systems in the central nervous system. About 60% of patients treated with them report side effects. The typical side effects in addition to those above are sedation, anticholinergic effects – for example, dry mouth

and constipation, weight gain, sexual dysfunction, metabolic changes - glucose intolerance, agranulocytosis – low white blood cell count, and hypotension – low blood pressure. Inherently with the disorder and the heavy side effects comes the problem of non-compliance: due to low insight in illness and delusions, up to 80% of patients do not take their antipsychotics as planned (Benkert et al., 2013; Möller & Müller, 2006). In addition to the side effects, about 25-30% of schizophrenia patients are drug resistant, so called non-responders. That is, despite continuous medication use, AVH do not improve (Möller & Müller, 2006; Shergill, Murray, & McGuire, 1998). Therefore, the search for new treatments outside the pharmaceutical realm is important and tDCS is one of the methods that has been proposed.

1.4.1 The hypofrontal/hypertemporal model

There are several models trying to explain how AVH arise. One is based on the idea that AVH occur due to bad or unwanted memories that get activated unintentionally as inner speech (Ralph E Hoffman, 1986; Waters, Badcock, Michie, & Maybery, 2006). Another AVH model is based on tinnitus research and states that AVH arise due to interhemispheric miscommunication, meaning that altered connectivity between the auditory cortices via the corpus callosum causes AVH (Ćurčić-Blake et al., 2017; Steinmann, Leicht, & Mulert, 2014). The source monitoring model hypothesizes that AVH arise due to deficits in self-monitoring and reality discrimination (Allen, Aleman, & Mcguire, 2007; Bentall & Slade, 1985). The following hypofrontal/hypertemporal model and the source-monitoring model have been combined into one descriptive model (Aleman & Larøi, 2011).

In the present thesis, the following model was chosen as it is the basis for the model of tDCS treatment in AVH (described below) and has been used extensively in the research of the Bergen fMRI Group owing to growing empirical support. The neuronal basis of AVH is hypothesized to be due to two main processes: First, language areas in the left temporo parietal cortex (TPC) are assumed to be *hyper*active, giving voice hearers the impression that self-generated stimuli are external stimuli. Second, *hypo*activation in the DLPFC aggravates AVH, because the

DLPFC is insufficiently capable of exerting top-down control over the hyperactive TPC (Hugdahl, 2009; Jones, 2008). This theory is based on neuroimaging findings showing that, on one hand, there was increased activation in the temporal lobe during hallucinations in the absence of external stimuli (Lennox, Park, Medley, Morris, & Jones, 2000; Shergill et al., 2004). On the other hand, studies had shown that schizophrenia patients with hallucinations, when presented with speech sounds, fail to activate the speech areas in the TPC in the same way as healthy controls (Hugdahl, Løberg, & Nygård, 2009). Later, findings by Kompus et al. (2011) confirmed this, showing that schizophrenia patients have increased activation in the left primary auditory cortex in the absence of external stimuli and decreased activation in the presence of external stimuli. This amounts to a hyperactivation in the TPC in schizophrenia due to internal stimuli, but also a reduced responsivity of the TPC to external stimuli, most likely due to top-down control impairment. Patients also fail to activate higher cognitive functions for executive control and top-down suppression and exhibit reduced gray matter density and volume in the left TPC (Hugdahl, Løberg, et al., 2009; Hugdahl, Løberg, Specht, et al., 2008). When glutamine and glutamate (measured combined as Glx) were measured in the temporal and frontal lobe, it was shown that schizophrenia patients had reduced Glx levels compared to healthy controls, while patients with severe hallucinations had increased Glx levels compared to patients with less frequent hallucinations in both regions of interest (Hugdahl et al., 2015). This evidence lends support to the hypofrontal/hypertemporal model depicted to the left in Figure 1 (Hugdahl, Løberg, et al., 2009).

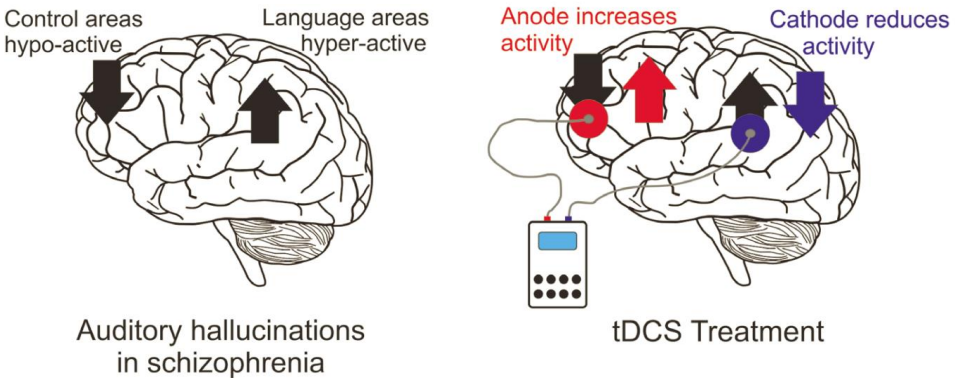

Figure 1 shows the proposed hypofrontal/hypertemporal model of auditory verbal hallucinations to the left and the hypofrontal/hypertemporal reversal model for tDCS treatment to the right.

1.4.2 The hypofrontal/hypertemporal reversal model

The aforementioned AVH hypofrontal/hypertemporal model leads us to the theoretical background of the present thesis. As described above, many tDCS studies and treatments are based on the assumption that the anode is excitatory, and the cathode is inhibitory. If true, then by placing the cathode over the assumed hyperactive language areas, activity in the TPC should be downregulated. In turn, by placing the anode over the assumed hypoactive cognitive control areas, activity in the DLPFC should be increased and cognitive control should be improved. This montage is designed to reverse the underlying neuronal effects of AVH caused by the hypofrontal/hypertemporal activation pattern. Hence, we call the idea that this reversal would reduce AVH the "hypofrontal/hypertemporal reversal model" (see right side of Figure 1); this is currently the leading theory behind the AVH treatment with tDCS.

A first randomized controlled trial (RCT) in 2012, which used the anode/DLPFC-cathode/TPC montage based on the hypofrontal/hypertemporal reversal model, was a great success: a significant reduction in AVH of around 40% (equivalent to an effects size of Cohen's d =1.6) after five consecutive days with 20 min twice-daily tDCS at 2 mA (Brunelin et al., 2012). Subsequent RCTs have shown

more inconsistent results for the effect of tDCS on hallucinations (Bose et al., 2017; Koops et al., 2018). Some replicated the significant decrease in AVH after 20 min of 2 mA real tDCS compared to sham tDCS after 10 sessions (Bose et al., 2017; Mondino, Haesebaert, Poulet, Suaud-Chagny, & Brunelin, 2015) and 40 sessions (Lindenmayer et al., 2019). However, tDCS was not always superior to sham, i.e., the placebo effect was as strong as the treatment effect of tDCS after 10 sessions (Koops et al., 2018) and five sessions (Fröhlich et al., 2016). Another study (Kantrowitz et al., 2019) found a significant reduction of AVH when controlling for medication. Others found a positive effect of tDCS on cognition after five sessions (Smith et al., 2015) and insight into illness (Chang, Tzeng, Chao, Yeh, & Chang, 2018) but no reduction of AVH. No effects for AVH measures were found in another study, but a reduction in negative symptoms was found (Valiengo et al., 2019). Neither unilateral nor bilateral tDCS at 2mA for 15 once-daily sessions reduced AVH in another study (Fitzgerald, McQueen, Daskalakis, & Hoy, 2014). After ten tDCS sessions over two weeks in the DLPFC, negative symptoms were reduced, while AVH specifically were not assessed (Gomes et al., 2015; Palm et al., 2016).

Several meta-analyses and reviews (Hasan, Strube, Palm, & Wobrock, 2016; Kubera, Barth, Hirjak, Thomann, & Wolf, 2015; Mondino, Sauvanaud, & Brunelin, 2018; Nathou, Etard, & Dollfus, 2019; Nieuwdorp, Koops, Somers, & Sommer, 2015; Pondé et al., 2017) suggested that the database is too small for a conclusion on the effectiveness of tDCS on AVH and that there is a need for further investigation on the impact of different stimulation parameters. AVH symptom reduction for active tDCS was found but not significant in another meta-analysis (Kennedy, Lee, & Frangou, 2018). Osoegawa et al. found tDCS to be superior to sham with Hedges g = 0.5 for the treatment of negative symptoms in schizophrenia (2018). Recent meta-analyses found a reduction for stimulation given twice daily and 10 or more sessions applied for auditory hallucinations (Cheng et al., 2020; J. Kim et al., 2019). The number of reviews (n = 12, two not cited here due to language, Dutch, and being outdated) on brain stimulation including tDCS for AVH is higher than the number of

empirical studies on the effects of tDCS on auditory hallucinations (n = 11), which also indicates a need for more original studies.

In addition to the unresolved question whether tDCS treatment in general is effective or not, we know even less about the specific mechanisms that underlie the tDCS treatment of AVH. For example, scientists have been calling for more basic research on the influence of tDCS on the stimulated brain tissue using neuroimaging (J. Kim et al., 2019). Most of the studies that used tDCS to treat AVH are based on the hypofrontal/hypertemporal reversal model (Bose et al., 2017; Brunelin et al., 2012; Chang et al., 2018; Fitzgerald et al., 2014; Fröhlich et al., 2016; Kantrowitz et al., 2019; Koops et al., 2018; Lindenmayer et al., 2019). However, very few of the RCTs on tDCS in AVH studies include neuroimaging. Two studies investigated the effect of stimulating the DLPFC alone - not the TPC - and both investigated only resting-state connectivity (Mondino, Jardri, et al., 2015; Palm et al., 2016). In general, neuroimaging studies in connection with tDCS mostly focus on the primary motor cortex and are usually limited to one specific neuroimaging method, not multimodal imaging. Hence little is known about the underlying mechanisms of tDCS, especially in other brain regions. For this reason, the present thesis employed multimodal neuroimaging of the hypofrontal/hypertemporal reversal tDCS montage, in order to study its underlying mechanisms.

1.4.3 Dichotic Listening paradigm

Dichotic listening is a task where two different consonant-vowel syllables (such as /ta/ and /da/) are presented simultaneously, one to the left and one to the right ear. There are three different conditions: In the non-forced condition, participants are instructed to verbally report the syllable they heard best and most clearly. In the forced-left and forced-right condition, they are instructed to specifically report the stimulus from the left and right ear, respectively, adding an attentional focus to the paradigm. This task was chosen because it has previously been shown to produce reliable activation in the DLPFC and TPC areas (van den Noort, Specht, Rimol, Ersland, & Hugdahl, 2008). The non-forced condition typically

evokes areas in the TPC regions (van den Noort et al., 2008), while the attentional focus leads to activations in the cognitive control regions (Hugdahl, Westerhausen, et al., 2009). Moreover, healthy individuals typically display a right ear advantage behaviorally, meaning that, when asked to report the stimulus they perceived best or most clearly, they more often report the one presented to the right ear than the left ear. This is indicative of left-hemispheric language lateralization (Kimura, 1961).

This right ear advantage is reduced in patients with schizophrenia (Hugdahl, Løberg, Jørgensen, et al., 2008; Kompus et al., 2012), especially in those with frequent and severe AVH (Ocklenburg, Westerhausen, Hirnstein, & Hugdahl, 2013). Schizophrenia patients are also less able to attend to the stimulus presented in one particular ear (Collinson, Mackay, Jiaqing, James, & Crow, 2009). All these features make dichotic listening a useful paradigm to study DLPFC/TPC activity and schizophrenia patients, especially those with auditory hallucinations.

1.4.4 Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI), like all other MRI techniques, is based on nuclear magnetic resonance (NMR). In ^{1}H-NMR the magnetic properties of hydrogen atoms are used to produce pictures of the body. Hydrogen atoms consist of one proton (- charged) and one (+ charged) electron. The proton possesses a spin and therefore has a magnetic moment. When the proton is placed in a strong external magnetic field (B_0), such as an MRI scanner, the spins of the protons align with the magnetic field and undergo precession. The precession frequency is directly proportional to the applied magnetic field (B_0) and is called Larmor frequency; this is given by the Larmor equation:

Eq 1: $$\omega_0 = \gamma_0 B_0;$$

Where ω_0 is the Larmor frequency in megahertz, γ_0 is the gyromagnetic ratio, a constant specific to a particular nucleus (~42.577 MHz/T for ^{1}H), and B_0 is the strength of the magnetic field in Tesla. The protons can align either parallel or anti-parallel to the magnetic field, with parallel alignment being slightly more common

because this state requires less energy. This small difference between the number of spins being parallel and anti-parallel gives a net magnetization in the longitudinal direction that can be measured. A radiofrequency (RF) pulse with the same frequency as the Larmor frequency is transmitted in order to make the spins absorb energy; this is called excitation. A 90 degree RF pulse, flips the longitudinal magnetization into transverse magnetization. Now, the spins precession is around the z-axis and works as an electrical generator. Thereby, the rotating spins induce an alternating field which can be picked up by a receiver – the MR signal (Weishaupt, Köchli, & Marincek, 2008). This is a fundamental principle that applies to all MRI methods, including fMRI.

fMRI allows for observation of active brain areas in a non-invasive manner and was discovered thirty years ago by Ogawa et al. (1990). The fMRI technique is based on the blood-oxygen-level dependent (BOLD) contrast; it is measured via deoxygenated hemoglobin, hemoglobin without an attached oxygen, which is paramagnetic (attracted to a magnetic field) and alters the magnetic susceptibility of blood (Buxton, 2013). When neuronal activity occurs, there is an increased glucose metabolism and therefore an increased oxygen demand. Hence, the blood flow to the active area increases to compensate, which increases the amount of available oxygenated hemoglobin while the proportion of deoxygenated hemoglobin decreases, giving an increased MRI signal. This mechanism is called the hemodynamic response. fMRI is an artefact prone method and in order to minimize artefacts, especially movement artefacts, participants need to be well briefed on lying as still as they manage and feel secure. The signal that is measured – the increase in oxygenated hemoglobin - is very small, only 1%, which is why the signal-to-noise-ratio is another difficulty of the method (Poldrack, Mumford, & Nichols, 2011; Strubreither et al., 2011).

There is 5-6 seconds delay between the actual neuronal activity and the observed peak hemodynamic response. The peak is followed by an undershoot that does not return to baseline for about 20 seconds, which is the reason for the relatively low temporal resolution of fMRI (Poldrack et al., 2011). It is important to keep in

mind that fMRI is not a direct measure of neural activity as there are various physical, physiological, and anatomical parameters that affect the BOLD signal. Between the neural activity and the change in MR signal there are many steps, such as increased oxygen-extraction rate and cerebral flood flow, overcompensation by oxygenated blood, decreased deoxyhemoglobin concentration and a change in magnetic susceptibility (Faro & Mohamed, 2010).

In order to analyze fMRI data there are three essential steps; correction – for motion and distortion, normalization – the alignment of the individuals data to a common spatial framework, smoothing – in order to reduce noise the data is intentionally blurred (Poldrack et al., 2011).

fMRI data is typically acquired whilst a participant performs a simple cognitive or motor task in the scanner – often split into periods of activity separated by periods of rest. Contrasting images acquired during activity with those acquired at rest allows regions of increased (or decreased) activity to be identified.

1.4.5 Resting-state fMRI

Resting-state fMRI (rs-fMRI) does not require participants to perform any specific task, as opposed to paradigm- or task-based functional MR imaging and is thus carried out with participants at rest. It is also based on the BOLD signal fluctuation (Lv et al., 2018). It can be used to study brain activity at rest, described as the default mode network and brain function in general (Poldrack et al., 2011). The are several ways to analyze rs-fMRI data. In this thesis, seed-based functional connectivity analysis and fractional amplitude of low-frequency fluctuation (fALFF) were used. Seed-based functional connectivity finds regions correlated with the activity in a seed region by computing a cross-correlation between the BOLD signal time-series of the seed and the rest of the brain. “The coupling of activation between different brain areas indicates that they are involved in the same underlying functional process and can thus be interpreted as functionally connected. However, these brain regions may not be directly connected by neural fibers” (Lv et al., 2018).

fALFF is a measure showing relative BOLD signal power within the frequency band of interest (0.008-0.09 Hz in this study) compared to the entire frequency band and is defined as a ratio of root mean square of BOLD signal at each individual voxel after vs. before low- or band- pass filtering (Zou et al., 2008). fALFF is regarded as an indicator of spontaneous neural activity (Yu-Feng et al., 2007; Zou et al., 2008) since it coincides with other established activity measures (Kiviniemi et al., 2000) and shows the expected default mode network activity patterns during rest (Fransson, 2006; Zou et al., 2008).

1.4.6 Magnetic Resonance Spectroscopy

MR spectroscopy (MRS) is a method to identify and measure metabolite concentrations in the brain (De Graaf, 2019, p. 43). It provides the possibility to look for changes on the molecular level in the brain tissue, but it has limited spatial resolution (Hajek & Dezortova, 2008). In our studies, we used ^{1}H-MRS, which picks up the signal from hydrogen protons attached to other molecules in a specified region, our ROI, which is defined by a voxel (3-dimensional cuboid region). The MRS output, which is a spectrum made from the acquired time-domain data by Fourier transformation, shows distinct peaks at different radiofrequencies representing the proton nuclei in different chemical environments. A typical spectrum can be seen in Figure 2B in paper II, for example. Many neurotransmitters are too large or lack the necessary properties to be visible with in vivo MRS, but glutamate and GABA are possible to detect (Blüml, 2013).

Chemical shift is the main method by which peaks in the spectrum are assigned to different compounds. Electron density shields the nuclei, the nucleus “sees” a fractionally smaller magnetic field and slightly shifts the resonance frequency for protons in different molecules and within the same molecule, in accordance with the Larmor equation (Eq 1). The magnetic field is also modulated by J–coupling, an internal, indirect interaction of spins within the same molecule due to the electron structure, which results in a modulation of the signal intensity depending

on sequence type and parameters. Depending on how many spins are coupled and affecting each other via J-coupling, the observed signal gets split into several peaks.

The signal to noise ratio (S/N) is crucial for MRS and one of the biggest challenges with the method. It is the ratio between the amplitude of a resonance and the amplitude of random noise observed in the spectrum. The S/N and quality in general can be increased by a few parameters, such as longer acquisition time, minimal movement by the participant, larger volumes, good shimming (optimization of the homogeneity of the magnetic field at ROI), and shorter echo times (Blüml, 2013).

Water is the most abundant compound in tissues, which is why the majority of the received MRS signal comes from the two protons in water, providing a large resonance peak at 4.65 ppm. The concentration of metabolites is often >10 000 times lower than that of water, leading to baseline distortions and making accurate detection of metabolites challenging. In order to deal with this issue, the water signal is suppressed but not altogether removed (De Graaf, 2019, p. 317).

Point Resolved Spectroscopy Sequence (PRESS) is one of many MRS sequences. It needs one voxel or ROI and does not require addition or subtraction of signals. It uses slice selective pulses along each of the spatial directions: one 90° excitation pulse and two 180° refocusing pulses, generating a signal from the overlap in the form of a spin echo. It recovers the maximum possible signal unlike, for example, the STEAM sequence. This is an advantage because S/N is crucial for data quality (Blüml, 2013). Glutamine and glutamate may not be easily distinguished from one another with the PRESS sequence, but can be measured in a combined measure called Glx. Glutamate is the main excitatory neurotransmitter in the brain and is relatively abundant with 6-13 mmol/L concentration. Glutamine is synthesized from glutamate in astroglia and synthesized to glutamate in neurons in the glutamate-glutamine cycle. It is important for the metabolism within the cell and has a concentration of 3-6 mmol/L.

γ-Aminobutyric Acid (GABA) is the main inhibitory neurotransmitter in the brain and has a typical concentration of ca. 1 mmol/L. Glutamate is its precursor (De Graaf, 2019; Ramadan, Lin, & Stanwell, 2013). Due to its low concentration and overlap with stronger signals, GABA is not possible to estimate with a regular PRESS sequence. However, an editing sequence such as MEGA-PRESS sequence can be used; where additional pulses are used to manipulate signals from specific metabolites, with the difference between "edited" and "unedited" spectra allowing those metabolites to be separated (Blüml, 2013). In MEGA-PRESS, "unedited" PRESS spectra are subtracted from spectra acquired with an editing pulse at 1.9 ppm, which allows the coupled GABA peak at 3.0 ppm to be isolated.

In order to get most reliable estimates it is possible to perform segmentation, where the content of the MRS voxel is classified according to tissue class (e.g., cerebral-spinal-fluid, gray matter or white matter), and the spectroscopy data is corrected according to voxel content and the relaxation time of the different parts.

1.4.7 EEG and EMG

Electroencephalography (EEG) and surface electromyography (EMG) were used as measures to look at epileptic spikes and muscle jerks in the first study presented in this thesis. With EEG, one can non-invasively measure the brain's electrical activity via electrodes attached to the scalp. Summations of excitatory and inhibitory postsynaptic potentials are measured (Marquardt, 2015). In a clinical setting, one usually uses 19+2 electrodes set up in the international 10/20 system to diagnose: different encephalopathies, epilepsy, and sleep disturbance. The data from a clinical EEG setup was used in this thesis to quantify the number of epilepsy spikes before and after tDCS treatment. In research, more electrodes are usually used and the raw EEG data is processed in order to calculate event-related-potentials (ERP) These are specific wave-patterns hidden in the raw EEG that occur in the brain in relation to an event/stimuli and are used to study attention, error making and more in healthy participants and diseases (e.g., Eichele et al., 2017; Marquardt, Eichele, Lundervold, Haavik, & Eichele, 2018).

Surface EMG is a technique to study the electrical activity produced by skeletal muscles by placing electrodes over specific target muscles. Surface EMG with electrodes is used rather than needle electrodes for EMG, due to its non-invasive nature (Cacioppo, Tassinary, & Berntson, 2000).

2. Aims of the thesis

The overarching aim was to advance the clinical applications of tDCS by gaining a better understanding of its underlying neuronal mechanisms. The main objective was to test tDCS as treatment for auditory verbal hallucinations and to better understand its underlying mechanism, but as the opportunity arose treatment efficacy was also studied in epilepsy. The following research questions will be addressed:

1) Can tDCS reduce auditory hallucinations?

2) Is there supporting evidence for the hypofrontal/hypertemporal reversal model of the tDCS treatment?

3) What are the neurochemical and functional changes in the stimulated brain regions of tDCS treatment, in general?

4) Does tDCS relieve symptoms in POLG mutation specific epilepsy?

To answer those questions, we conducted three studies:

Paper I: In the first study, tDCS treatment was given to a single patient with a specific disease, namely status epilepticus induced by POLG-mutation. This addresses research question four.

Paper II: In the second study, we aimed to test the hypofrontal/hypertemporal model indirectly, by stimulating healthy individuals with the reversed electrode montage that is used in tDCS treatment of patients. That is, the supposedly excitatory anode was placed over the TCP and the supposedly inhibitory cathode over the DLPFC, in order to mimic the hypofrontal/hypertemporal model for AVH in healthy participants. To examine the underlying neuronal effects of tDCS we employed a multimodal approach, encompassing behavior, functional activity, and neurotransmitter levels in the same tDCS session. Participants received 2 mA tDCS for 20 min, the standard parameters for tDCS treatment in AVH (also used in the RCT in paper III). By investigating the effects of the reversed electrode montage in healthy individuals, we

also indirectly test the general idea that tDCS over the DLPFC and TPC leads to changes in those areas, as postulated by the hypofrontal/hypertemporal reversal model. Paper II thus addresses research questions two and three.
Paper III: In the third study, an RCT was carried out with patients with severe auditory verbal hallucinations, in order to examine *if* and *how* tDCS can reduce voice hearing. Also here, behavior, functional activity, neurotransmitter levels (as assessed by DL, fMRI and MRS respectively), and in addition functional connectivity and anatomical changes (as assessed by rs-fMRI and structural MRI, respectively) were measured before and after treatment to unravel the underlying mechanisms of tDCS (addressing research questions one to three). The study parameters were based on Brunelin et al. (2012), which have become standard procedure, with 20 min of 2 mA tDCS for 10 sessions. The anode was placed over the DLPFC and the cathode over the TPC in order to reverse the hypofrontal/hypertemporal activity pattern.

As a behavioral marker for DLPFC and TPC involvement the dichotic listening task was used in paper II and III. As described above, this is a well-established paradigm, that has repeatedly demonstrated (a) activation in the DLPFC and TPC (van den Noort et al., 2008), (b) reduced right ear advantage in schizophrenia patients compared to controls (Hugdahl, Løberg, Jørgensen, et al., 2008), and (c) a reduced ability in schizophrenia patients to report stimuli from a specific ear compared to controls (Collinson et al., 2009). We thus hypothesized that the reversed montage in healthy participants in paper II would mimic the deficits observed in schizophrenia patients and that the treatment in paper III would improve patients' performance. We hypothesized functional activity and Glx increase under the anode and functional activity decrease and GABA increase under the cathode in both paper II and III.

In this manner, we were able to thoroughly investigate tDCS treatment and its underlying neuronal mechanisms in a single clinical case, a population of healthy individuals and a specific patient group, namely AVH hearers, and thereby study the leading theory behind the AVH treatment with tDCS.

3. Methods

3.1 Participants

3.1.1 Paper I: tDCS in POLG epilepsy

In paper I, our participant was a young woman, age 15, with severe POLG epilepsy, who received tDCS as experimental emergency treatment due to medication resistance.

3.1.2 Paper II: Healthy participants

Thirty-eight participants were recruited via flyers and word-of-mouth, resulting mostly in participants being students from the Faculties of Medicine and Psychology at the University of Bergen. Exclusion criteria were past/present neurological or psychological disorders, head trauma, metallic implants, epilepsy in first degree relatives, pregnancy, claustrophobia, acute consumption of drugs or alcohol at time of testing, and severe skin diseases in the area of the electrode placement. After exclusion of six participants, the remaining 32 (18 males) had a mean age of 26±4.8 years. They received reimbursement for their participation and gave written informed consent.

3.1.3 Paper III RCT of tDCS treatment in AVH

Twenty-one participants underwent an RCT on tDCS treatment for AVH. Inclusion criteria were the following: 1) Able to give written consent; 2) Having hallucinations at least five times a week; 3) Two different antipsychotic drugs must have been tried which did not eliminate the hallucinations (medication resistant); 4) On stable medication for at least 2 weeks at project start.

Exclusion criteria were: 1) Being underage (under 18); 2) being under guardianship or mandatory mental health care; 3) Have metal in their body such as heart pacemaker, cochlea implant, medical pumps, surgical clips, brain implants/stimulators or metal in their head or eyes; 4) Have a skin disease such as

neurodermatitis on their head where the electrodes were placed or 5) being pregnant. 1) and 2) being ethical considerations, 3) and 5) being safety issues for MRI scanning and 4) being a safety issue for tDCS treatment.

3.2 Ethical considerations

For the **first study** the use of tDCS was discussed with Regional committees for medical and health research ethics (REK), who considered it a form of supplementary experimental treatment whose purpose was to provide care for an individual, and for which the caring physician could take responsibility without obtaining the committees' approval.

For the **second study** ethical approval was obtained by REK (2012/2217), the same is true for the **third study** (2014/2179 REK). For all patients included in the study, the treating physician determined that they were able to give consent, not the research staff. To ensure that patients understood that the treatment was experimental and part of a study, potential participants received oral and written information about the study. If they agreed to take part in the study, they signed the written consent form before the study started.

3.3 tDCS stimulation

For all three studies we used a binodal set-up with anode and cathode on the scalp. Stimulation was delivered by a NeuroConn stimulator. Two rubber electrodes (5x7cm^2) were used, and 2 mA stimulation lasted for 20 minutes in each session (additional ramp up and down 30 seconds), giving a current density of 0.057 mA/cm^2.

In the **first study**, the electrode montage was: cathode over the left motor cortex (EEG 10/20 system: C3) and the right orbitofrontal cortex (Fp2) and treatment was given for five consecutive days (Figure 2). The electrodes were prepared with a 9 mg/ml NaCl solution saturated sponge and coated with electrode paste (Signa gel electrode gel, BIOPAC Systems Inc., Santa Barbara, California, US). There was no sham condition in this case study.

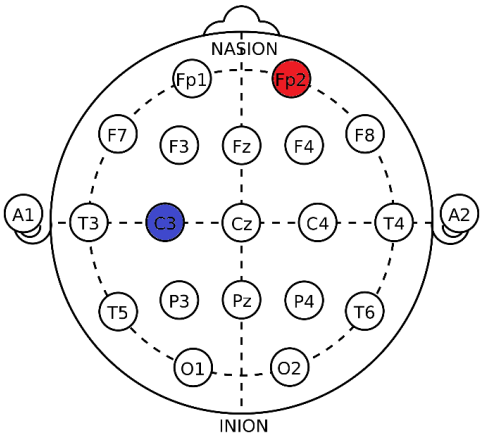

Figure 2 tDCS montage study I.

For the **second study**, the anode was placed over the left TPC and the cathode over the left DLPFC (Figure 3). The stimulator was set to study mode to ensure double blinding: that is, codes had to be entered by the experimenters that would either provide real or sham stimulation. Participants were tested twice, once with real and once with sham stimulation in a double-blind design, with a range from 4-16 days in between. In the sham case, stimulation was delivered for 40 ms to provide the sensation of being stimulated. An MRI compatible tDCS system (DC-Stimulator Plus from NeuroConn GmbH, Ilmenau, Germany) was used. The electrodes were coated with a more adhesive paste Ten20 (Weaver and Company, Aurora, United States of America). Correct placement for the electrodes was determined with EEG caps in 10/20 system at AF3 and CP5 (EasyCap, Herrsching, Germany) and side effects were measured with the tDCS Adverse Effects Questionnaire.

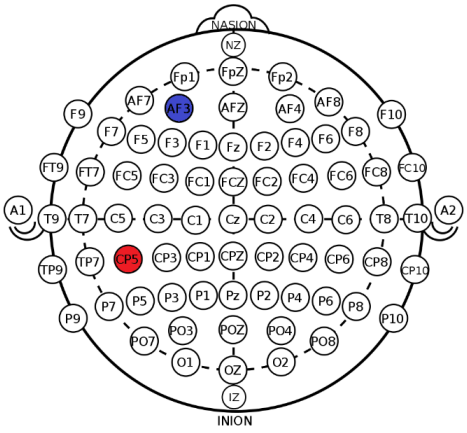

Figure 3 tDCS montage study II.

In the **third study**, tDCS was given for five consecutive days, twice daily with a minimum break of three hours in between. Participants would either receive sham or real tDCS for the entire treatment in a double-blind design. The cathode was placed over the left TPC and the anode over the left DLPFC (Figure 4). The electrodes were prepared with a sponge saturated with saline solution and coated with electrode paste like in study I. Correct placement for the electrodes was determined with EEG caps at AF3 and CP5 and side effects were measured, like in study II.

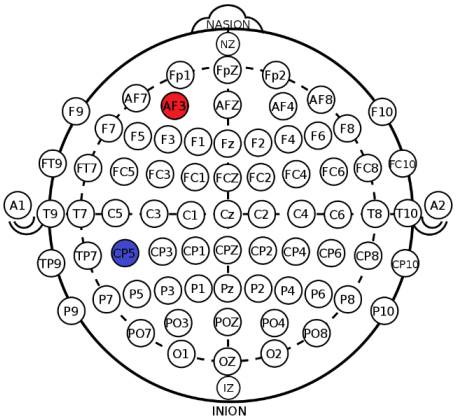

Figure 4 tDCS montage study III.

3.4 Study protocols

3.4.1 Paper I

20 min before, 20 min during, and 20 min after four of the five tDCS sessions, surface electromyography (EMG) was recorded to measure tDCS effect on the muscle jerks. Before and after tDCS the electroencephalography (EEG) was recorded to measure the frequency of spikes. On one day, the EMG/EEG system was not available.

3.4.2 Paper II

Participants completed two MRI sessions during which tDCS took place, one session with real and one with sham tDCS (for details please see Figure 1 in paper II). Table 2 shows all MRI sequences included in the study in chronological order. Voxel I and voxel II were the left TPC or the left DLPFC (counterbalanced across participants).

Table 2

Chronological order of MRI sequences included in each session

MRI sequence	**Time (min:sec)**
Structural MRI	4:00
MRS PRESS in Voxel I	03:48
MRS PRESS in Voxel II	03:48
DL with tDCS, fMRI sequence	16:03
MRS PRESS in Voxel I	03:48
MRS PRESS in Voxel II	03:48

DL – dichotic listening, fMRI-functional magnetic resonance imaging, min – minutes, MRI – magnetic resonance imaging, MRS- magnetic resonance spectroscopy, sec – seconds.

MRS

We used a *Point resolved spectroscopy sequence (PRESS)* with TE = 35ms, TR = 1500ms, and 128 repetitions (with eight additional water-unsuppressed "reference" frames), with a sample frequency of 5000 Hz and the number of samples was 4096. One voxel was placed over the left DLPFC (27x25x32mm, volume 21,6 mL) and the other over the left TPC (26x31x31mm, volume 25,0 mL). After acquisition, the data were quantified with LCModel version 6.3-1J (Provencher, 1993), using a basis set incorporating components from 15 metabolites: alanine, aspartate, creatine, γ-aminobutyric acid, glucose, glutamine, glutamate, glycreophosphorylcholine, phosphorylcholine, lactate, myo-inositol (mI), N-acetylaspartate (NAA), N-acetylaspartylglutamate, scyllo-inositol, and taurine.

Metabolite estimates were scaled to an internal water reference, then adjusted for partial volume effects, water concentration, and expected relaxation times in different tissue classes (Gasparovic et al., 2006). Voxel tissue content was estimated from the structural T1 images, after segmentation into distinct tissue classes (gray matter, white matter, cerebrospinal fluid) using per-subject voxel masks. Spectral and fit quality was ensured by visual inspection, with attention to linewidth, S/N and

Cramér Rao Lower Bounds of individual estimates, and aberrations in baseline or residual signals.

Dichotic Listening paradigm

During tDCS, participants completed a 16 min long dichotic listening paradigm that was adopted to fMRI. It started 3.5 minutes after tDCS had begun to ensure the left TPC and DLPFC had already been stimulated for a while. In every dichotic listening trial, two out of six different syllables (/ba/, /da/, /ga/, /pa/, /ta/, and /ka/) were presented simultaneously, one to each ear. For example, /ba/ to the left ear and /ka/ to the right ear. Homonyms (e.g., /ba/-/ba/) were not included, leaving 30 possible syllable combinations which participants completed twice, in three different conditions: the non-forced condition, the forced-left and forced-right condition. Verbal responses were written down and recorded during scanning as a measure of behavioral data.

The dichotic listening paradigm was carried out in a block design during fMRI acquisition. The paradigm had 270 volumes in total, distributed across 25 blocks (7 resting-blocks +6 Non-Forced +6 Forced-Right +6 Forced-Left). The block order was pseudo-randomized. Each block was 10 trials long, giving 180 dichotic listening volumes/trials and 70 resting volumes (Hugdahl & Andersson, 1986; Hugdahl, Westerhausen, et al., 2009; Thomsen, Rimol, Ersland, & Hugdahl, 2004). Following each volume a silent gap was given for presenting the stimuli and recording the verbal responses from the dichotic listening task (van den Noort et al., 2008). Participants waited quietly for 90 seconds until tDCS finished, after the dichotic listening task.

fMRI

The dichotic listening paradigm was carried out in a block design during fMRI acquisition, using a 2D gradient echo-planar imaging sequence with the following parameters: TE = 30 ms, nominal TR = 3500 ms (1500ms nominal acquisition+2000ms “silent gap”), flip angle = 90 degrees, 64x64 matrix, FOV =

220mm, 27 axial slices of 5mm thickness with 0.5mm gap. Stimuli were presented with E-Prime 2.0 Professional.

The fMRI data was preprocessed using SPM12 by realigning and unwarping the data to correct for movement and related image distortions, normalization into the MNI standard reference space, and smoothing with an 8mm Gaussian kernel in order to improve SNR. The data were visually inspected for remaining motion artefacts. The first four dummy scans were cut from subsequent analysis. First level analysis was done for each participant and session by specifying a general linear model that incorporated the onsets of the stimulation blocks of the three conditions and included the realignment parameter as regressors of no interest and a high-pass filter set at 340 Hz. Contrasts were defined for exploring the effect of each condition (non-forced, forced-right, forced-left) separately.

Simulation of tDCS electrical field was carried out with a software called SimNIBS. To run the model, the electrodes in the simulation were placed over the real electrodes visible on each participant's head model. The simulated electrodes were $5\times7cm^2$, like the real ones, with a 1mm electrode thickness and 3mm gel. The electric field strength (in [V/m]) and the focality (in cubic mm) of the stimulation were calculated for the entire cortex and the peak activation field (10mm sphere).

3.4.3 Paper III

A double-blind RCT was carried out in patients with severe AVH to study tDCS treatment. Neuroimaging and clinical/neurocognitive assessment were run at baseline, post-treatment, and 3-month follow-up (Table 3), with 10 sessions tDCS between baseline and post-treatment. Table 4 depicts the list of clinical assessment and neurocognitive testing included in the study.

Table 3

Overview of the procedure and timeline of the RCT

		Randomized Control Trial			
	Pre-study assessment	**Day 1** **Baseline**	**Day 2 to 5**	**Day 6** **Post-treatment**	**3 months** **Follow-up**
tDCS treatment			2x daily 20 min of 2mA tDCS	2x 20 min 2mA tDCS	
Clinical examination	tDCS check-list, screening questionnaire, Medication	Hearing test	Adverse Effects Questionnaire	Adverse Effects Questionnaire	
Hallucination assessment		AHRS, QPE, PANSS		AHRS, QPE, PANSS, AHCS	AHRS, QPE, PANSS
Neuroimaging		Session 1: structural MRI, MR spectroscopy, Resting state fMRI, dichotic listening fMRI, ASL.		Session 2: structural MRI, MR spectroscopy, Resting state fMRI, dichotic listening fMRI, ASL.	Session 3: structural MRI, MR spectroscopy, Resting state fMRI, dichotic listening fMRI, ASL.
General functioning and neurocognitive abilities	Pre-study Questionnaire, Informed consent	AES, NART, CGI, GAF, Stroop, TMT, General Information Questionnaire, Expectations Questionnaire		AES, CGI, GAF, Stroop, TMT	AES, CGI, GAF, Stroop, TMT, Blinding Check Questionnaire

AHRS - Auditory Hallucination Rating Scale, AES - Apathy Evaluation Scale, PANSS - Positive and negative symptom scale, QPE - Questionnaire of psychotic experiences, CGI - Clinical Global Impression,GAF - Global Assessment of Functioning, Stroop - Stroop test, TMT - Trail Making Test, NART - National Adult Reading Test, AHCS- auditory hallucinations change scale

Table 4

List of clinical assessment and neurocognitive testing tools

Safety Questionnaires:
Pre-Study Questionnaire
Pre-Study tDCS/neuroimaging Checklist
Informed consent form
Expectations Questionnaire
Clinical assessment:
AHRS - Auditory Hallucination Rating Scale
AHCS – Auditory Hallucination Change Scale
AES - Apathy Evaluation Scale
PANSS - Positive And Negative Symptom Scale, semi-structured interview
Neurocognitive and General Functioning Assessment:
CGI - Clinical Global Impression
GAF - Global Assessment of Functioning
Stroop test
Trail Making Test
NART - National Adult Reading Test

Table 5 shows all MRI sequences in a single testing session in chronological order. Voxel I and voxel II were the left TPC or the left DLPFC, which were alternated between participants and sessions. It was counterbalanced across participants whether MRS PRESS or MEGA-PRESS was measured first. The analysis of MRS, fMRI and the dichotic listening task are highly similar to paper II (described above) and are described in detail in the paper. For structural MRI, parcellation of the cortical surface was performed using Freesurfer 5.0 (Fischl et al., 2004) to yield estimates for surface area, cortical thickness, and gray matter volume for each of the 74 labelled regions per hemisphere of the Destrieux atlas (Destrieux,

Fischl, Dale, & Halgren, 2010). Twelve regions of interest, based on electrode placement over the DLPFC and TPC, were selected and analyzed.

rs-fMRI was acquired for 5 minutes with closed eyes. The data was preprocessed and went through a default denoising procedure in the toolbox CONN. Seed-based functional connectivity analyses in addition to a Fractional Amplitude of Low-Frequency Fluctuations (fALFF) analysis were conducted. Two seed regions of interest were generated from the MRS voxel masks in the left DLPFC and TPC. tDCS treatment groups were compared in different contrasts. For seed-to-voxel connectivity and fALFF, a cluster correction procedure at the single-voxel level was applied with thresholds of $p<.001$ and $p<.005$, respectively. For both, the cluster level threshold was $p<.05$ with FDR-correction for multiple comparisons. The simulation of the electrical field of tDCS was carried out based on the structural data, similar to paper II, only here the EEG 10/20 virtual cap in SimNIBS was used to place the anode over AF3 and the cathode over CP5. The simulated electrodes were $5x7cm^2$, like the real ones, with a 1 mm electrode thickness and 8 mm sponge.

Participants in the sham group were offered to receive real tDCS after the completion of the study.

Table 5

Chronological order of MRI sequences in each MRI session

MRI sequence	**Time (min:sec)**
Structural MRI	07:07
MRS PRESS voxel I	03:48
MRS MEGA-PRESS voxel I	10:12
MRS PRESS voxel II	03:48
MRS MEGA-PRESS voxel II	10:12
Resting-state fMRI	05:30
Dichotic listening and fMRI	08:28

3.5 Statistical Analysis

In **paper I,** EMG and EEG spikes were counted manually by three raters. The counts were analyzed with an ANOVA and non-parametric Friedmann test for EMG data and paired sample t-test and non-parametric Wilcoxon tests for EEG spikes. Non-parametric statistical tests were used in addition as the counts were in a small range and not normally distributed.

In **paper II,** water-scaled, tissue-content-adjusted Glx levels from LCModel were subjected to a 2x2x2 repeated measures ANOVA with the within-participants factors Stimulation (real/sham), Time (before/after tDCS) and Brain area (DLPFC/TPC).

Correctly identified syllables from dichotic listening were transformed into accuracy rates and subjected to a 2x3x2 repeated measures ANOVA with the within-participants variables Stimulation (real/sham), Dichotic Listening Condition (non-forced, forced-right, forced-left) and Ear (left/right). Similarly, for the fMRI group analysis, individual contrast images were subjected to a 2x3 repeated measures

ANOVA with Stimulation (real/sham) and Dichotic Listening Condition (non-forced, forced-right, forced-left). For the electric field and focality *M*s and *SD*s were calculated.

In **paper III,** t-tests and Chi-square /Fischer exact tests were calculated for baseline comparisons between the groups and demographic variables, showing a difference in AHRS score between the real and sham group. As a result, AHRS score was included as a covariate in all further analyses.

The clinical and structural data were analyzed in a 2x3 repeated measures ANOVA with the within-participants variables *Time* (baseline/post- treatment/ follow-up) the between participant factor *tDCS Treatment* (real/sham). A 3x2x2 ANOVA of Glx and GABA levels was carried out with the within-participants variables *Time* (baseline/ post-treatment/ follow-up) and *Brain area* (DLPFC/TPC). *tDCS treatment* (sham/real) was added as a between-participant factor. rs-fMRI was processed in a toolbox called CONN; different contrasts were explored and post-hoc t-tests were done with extracted values. Correct responses from dichotic listening were transformed into accuracy rates and a 3x3x2x2 repeated measures ANOVA with the within-participants variables *Time* (baseline/post- treatment/ follow-up), *Dichotic Listening Condition* (non-forced/forced-left/forced-right), and *Ear* (left/right) as well as *tDCS Treatment* (real/sham) as a between-participant factor was performed. For fMRI, the group analysis was conducted in the SPM12 toolbox for individual contrast images a 2x3 repeated measures ANOVA was performed, with *tDCS Treatment* (real/sham) and *Time* (baseline/ post-treatment/ follow-up). For the electric field and focality *M*s and *SD*s were calculated. Finally, Correlations between the AHRS and neuroimaging variables were calculated.

4. Results

4.1 Paper I

The five consecutive days of tDCS treatment at 2 mA for 20 min did not lead to a statistically or clinically significant reduction of myoclonus jerking or epilepsy spikes in the 15-year old POLG patient.

4.2 Paper II

fMRI and dichotic listening did not show any tDCS related changes but yielded the typical activation of the auditory cortex in dichotic listening.

MRS results showed a trend with Glx levels being higher after tDCS than before when participants received real tDCS ($F_{(1,31)} = 3.35$, $p = .077$, $\eta^2_p = .098$). However, post-hoc tests were not significant. Further, this trend was not electrode specific, meaning the trend was unspecific to the brain area TPC or DLPFC. There was no significant three-way interactions between pre-post tDCS, brain areas TPC and DLPFC and real or sham stimulation in MRS.

Simulation of tDCS showed large individual differences and peak electric field strength between the electrodes, not as hypothesized directly under the electrodes. None of the calculated correlations, between Glx and dichotic listening or simulated electric field strength were significant.

4.3 Paper III

There was a small decrease in AVH which was shown both in the self-report measures of AHRS and AHCS. The AHRS scores AVH severity with seven questions. While the AHCS was used after treatment, simply asking if AVH became better, worse or were the same and how much if they became better or worse (in %). AHRS scores showed a post-treatment reduction: 12% real tDCS 15% sham tDCS group, and a follow-up reduction: 21% real tDCS 12% sham tDCS group, and the AHCS showed AVH reduction of 25% in the real and 22% in the sham group.

However, this decrease is only based on self-report measures and is not reflected interview-based measures as the PANSS. It was also evident that the treatment had a placebo effect and that the real tDCS effect was not much stronger than this placebo effect in our sample.

None of the neuroimaging data showed significant effects for the DLPFC or TPC, neither rs-fMRI, MRS, structural MRI nor task-related fMRI. We found a negative connectivity in the left and right superior frontal gyrus after treatment, which was not present at baseline. However, this was independent of real or sham tDCS. In the real tDCS group, there was a decrease of brain activity in the right precentral gyrus from before to after treatment, which did not emerge in the sham group. Note, that this does not include any of the two stimulated brain areas. Moreover, this finding was significant at a single-voxel threshold of .005 ($p_{size\ \text{p-FDR}} = 0.047$) but would not withstand the standard single-voxel threshold of .001. These data thus did not confirm the notion that tDCS reverses the hypofrontal/hypertemporal activity pattern.

For all three papers, more results can be found in the papers themselves.

5. Discussion

This thesis studied the underlying mechanism and effects of tDCS in a single case of POLG mutation induced epilepsy, in a healthy population, and a patient population of AVH hearers. We found no effects of tDCS treatment in the POLG epilepsy case. In the healthy participants, there were no tDCS effects on behavior or brain activity, and only an electrode-unspecific trend in Glx levels. In the AVH patients, a small clinical effect on AVH was found. However, there were no tDCS effects in the regions of interest in neuroimaging. Here follows a discussion of the individual papers and on more overarching topics concerning tDCS treatment and its underlying neuronal effects.

5.1 Paper I Case report: tDCS treatment for epilepsia partialis continua in POLG disease

This case study was conducted as an experimental treatment based on only one previously published case report (Ng et al., 2018). The epilepsy spikes and muscle jerks were not reduced by tDCS treatment and the young patient died 9 months after the tDCS intervention due to a super-refractory status epilepticus, demonstrating the severity and fast-moving nature of this particular POLG-disease case. We discuss several possibilities why the treatment did not work in the paper, one being that tDCS treatment was attempted too late in the course of the disease. The vicious cycle, starting with the POLG mutation, leading to dysfunctional mitochondrial DNA, causing failure in the respiratory chain, giving low neuronal energy levels in turn, eventually triggering seizure activity/ epilepsy and ultimately neuronal necrosis (Hikmat et al., 2017) might have been too far advanced in this case.

Another reason why we did not replicate the previous study might be that Ng et al. treated with tDCS for 14 days with the cathode over the temporo-parietal-occipital junction, while we only had five days of treatment over the left primary motor cortex, due to the fact that the patient having severe muscle jerks in her right arm. In addition, the two patients also had different genetic mutations. POLG disease

is quite rare and there are too few studies to prove whether tDCS is an effective treatment in this specific condition or not. But we were able to contribute to the very thin empirical database on this disease and tDCS so far, albeit in a fairly limited way, with one patient. The literature now comprises one case report where treatment worked (Ng et al., 2018) and one where it did not (Marquardt et al., 2019), neither being able to prove or disprove the efficacy of tDCS using case report design. In general, however, tDCS has been rated “probably effective” for decreasing seizures in epilepsy (Fregni et al., 2020).

5.2 Paper II Multimodal neuroimaging study of tDCS in healthy participants

There were no effects of tDCS on behavior and functional activity and only a trend towards a Glx increase after tDCS. In the paper, we discuss many details of the study, one is that we failed to detect significant tDCS effects because the peak of the electric field was between the two electrodes, and not in the targeted left DLPFC and TPC itself. While this could explain the lack of clear Glx results, it is difficult to reconcile with the fact that we did not observe any changes in functional activity in the left central sulcus/Broca's area.

The null findings are supported by findings in the literature that a single session of tDCS, like in our study, is not sufficient to induce changes in cognitive tasks in healthy individuals (Horvath, Forte, & Carter, 2015). Meta-analyses showed that cathodal tDCS over the DLPFC has little effect on cognitive tasks (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016) and that the cathode rarely induces inhibitory effects in cognitive tasks (Jacobson, Koslowsky, & Lavidor, 2012). Taken together with earlier tDCS research (D'Anselmo, Prete, Tommasi, & Brancucci, 2015; Dwyer et al., 2018; Westwood, Olson, Miall, Nappo, & Romani, 2017), paper II suggests that at least the posterior temporal-parietal region might be less responsive to tDCS than, for instance, the primary sensory/motor cortex and that it might be interesting to research Broca’s area with the DLPFC/TPC electrode montage.

5.3 Paper III Multimodal neuroimaging of tDCS treatment in patients with severe AVH

In paper III neither brain activity (as assessed with task-related and resting-state fMRI), brain structure, nor Glx/GABA levels showed significant effects of tDCS in the DLPFC or TPC, and none of those parameters correlated with changes in AVH over the course of the treatment. Thus, our data is not in line with the hypofrontal/hypertemporal reversal model, the leading theory behind the AVH treatment with tDCS.

The small treatment effect on AVH that was found in paper III was very similar at post-treatment between the sham (AHRS reduction 15%) and real (AHRS reduction 12%) group and got stronger at the 3-month follow-up in the real tDCS group (21% in real, sham 12% in sham). The positive effect on AVH was smaller in our sample than in some previous studies (Brunelin et al., 2012; Lindenmayer et al., 2019) but of similar magnitude as in Koops et al. (2018), who did not find improvements beyond placebo. This discrepancy could be explained by the fact that both Brunelin et al.(2012) and Lindenmayer et al. (2019) tested samples with schizophrenia patients only, while we and Koops et a. (2018) had a mixed sample. The most recent meta-analysis on tDCS in psychiatric disorders concludes that the DLPFC and TPC montage is probably effective (level B categorization) (Fregni et al., 2020). To reach a verdict on whether it is definitely effective (level A), more data is needed. Our study adds some data to this pool, but probably larger samples are needed, ideally from multicenter trials and/or collaborations across research groups.

Previous studies showed beneficial effects of tDCS on negative symptoms in schizophrenia with prefrontal stimulation (Gomes et al., 2015; Palm et al., 2016). This was not confirmed in our study, which was designed to pick this up, if present, with the full PANSS interview. The reason for this difference could be the difference in montage, as the other studies lack the TPC electrode. However, recently Valiengo et al. (2019) found a significant reduction in negative symptoms, but not AVH in schizophrenia with the same montage as ours. The difference here could be due to the

fact that Valiengo et al. recruited patients specifically with a negative symptom load. Fregni et al. (2020) concluded that tDCS is “probably effective” (Level B) for negative symptoms.

Another argument for multicentre collaborations is the identification of factors that determine treatment response. In our study, we found a small tDCS effect on AVH. Though not reported in the paper, the treatment effect rested mostly on three individuals in the tDCS group who improved by at least 50% according to the AHCS, while six participants did not improve (0%) and two only improved slightly (25-30%). Simply put, one can divide the sample into at least two groups, tDCS responders and tDCS non-responders. Why some patients responded well and others not at all and what distinguished these two groups needs to be further explored. This work has started and recently, Mondino et al. (2020) modeled the electric field in responders (n = 6) and non-responders (n = 11) and found that tDCS responders displayed a higher electric field strength in the left transverse temporal gyrus.

In addition to the treatment effect, there was a small decrease in fALFF measured brain activity in the right precentral sulcus in the real tDCS group. This is in the area of the primary motor cortex controlling the face. A possible explanation for this effect could be callosal inhibition/facilitation: The corpus callosum connects the two hemispheres and regulates communication between them (Mangia, Ursino, Lannocca, & Cappello, 2017). It was shown that excitation of one sensorimotor area leads to inhibition in the other and vice versa (Mangia et al., 2017). Thus possibly, the stimulation of the left frontal lobe could have led to corresponding activity changes in the contralateral, homologous area, whereby an increase in one hemisphere is associated with a decrease in the other hemisphere, and vice versa. However, without further investigations this is purely speculative.

We also found a negative connectivity cluster in the left and right superior frontal gyrus with the TPC. However, this was independent of whether participants received real or sham tDCS. The connectivity cluster was not present at baseline and only emerged at post-treatment. This anti-correlation would be in line with the notion

that, for example, an upregulation in the right/left superior frontal gyrus activity is associated with a downregulation in the TPC, as the hypofrontal/hypertemporal model would predict. But since it is not only apparent in the tDCS group but also the sham group, it is not in line with the hypofrontal/hypertemporal reversal model – and could be attributed to the placebo effect.

Both the tDCS simulation in paper II and III showed that the strongest electric field lies between the electrodes, in Broca's area. Broca's area function is linked to speech production, and stimulation here might improve speech production. In schizophrenia, this might help with the symptom of disorganized speech. Broca's area is involved in language processing and has been linked to AVH (Sommer et al., 2008). Hence, it could be speculated that the tDCS treatment effect also has to do with Broca's area stimulation. As described above, it was shown that tDCS responders had a significantly stronger electric field strength in the left transverse temporal gyrus (or Heschl's gyrus) compared to non-responders (Mondino et al., 2020), which is relatively close to Broca's area, but separated from it by the lateral fissure. Both regions are involved in language processing and have been found important in AVH (Ćurčić-Blake et al., 2012; Mondino et al., 2020). The effect of the DLPFC/TPC montage on Broca's area should be further investigated. While we did not see any fMRI activation here, it was not investigated with MRS to look for neurotransmitter changes and our research group just set up a study where this tDCS montage is investigated with functional MRS in healthy participants. There are also plans to study patients in the long term. Another implication of our finding that the current peaks over Broca's area, is that in order to specifically stimulate the left DLPFC and TPC another electrode set-up would be necessary. What this set-up would look like and what its effects on AVH would be also requires future studies.

When treating patients on antipsychotics with tDCS one needs to consider that the baseline cortical excitability is different in people using pharmacotherapy, that interferes with chosen tDCS dosage (Brunoni et al., 2012). In schizophrenia, the cortical excitability is lower than in controls in the motor cortex, either due to schizophrenia itself or antipsychotic medication, which means a higher stimulus

intensity is required in order to evoke motor response (Soubasi et al., 2010). It is not given that our regions of interest react the same way as the motor cortex, but if they do, this means we need higher intensity current in order to stimulate schizophrenia patients as compared to healthy individuals. This is complicated since stimulation with more than the conventional 2 mA can be painful and is not used in research.

As indicated above, certain individuals felt they benefited a lot from the treatment. Patients who participate in studies oftentimes want to continue the treatment, if possible, at home (Sandran, Hillier, & Hordacre, 2019); during this study we received several such enquiries. Unfortunately, we were not able to offer additional tDCS treatment, as we did not have a mandate for more stimulation than the 10 sessions in the RCT. However, our research group is working on ideas to implement tDCS at the psychiatric clinic. Researchers have been wary of advising the use of tDCS at home due to safety concerns, as we were when our patients asked. However, some of them were so convinced about the efficacy of the treatment that they bought a device anyway, against our recommendations. The use of tDCS devices at home and coverage about the method in the media is spreading and is therefore an ongoing debate in the brain stimulation community (Dubljević et al., 2014). In some cases, it is sold as a "wonder" device online to help with everything from training more efficiently to gaming better. For a long time, there was a disjoint between the regulation and guidelines which were mostly for scientific readers and the availability of tDCS devices for the public online (Dubljević et al., 2014). Recently, guidelines for home-based tDCS use have been developed (Charvet, Shaw, Bikson, Woods, & Knotkova, 2020), which can advance the safe use of tDCS in the private sphere. A review on in-home transcranial electric stimulation in psychiatric and neurological disorders showed that the field is advancing and that in-home stimulation seems so be safe. However videoconferencing is advisable to improve protocol compliance (Sandran et al., 2019). Only one of the studies included in the review was on schizophrenia, however. The cognitive deficits often accompanying schizophrenia might be an additional difficulty for safe in-home delivery of tDCS.

In science, the researcher wants to be as objective and as independent of their measurements as possible. However, as one measures and looks at what one studies, one also takes part in it and changes the reality of it (Matthews, 2014). We cannot be independent of our measurements. In our experiments this became very clear as we work with and study humans. First of all, we gave patients hope to become better – which can induce a placebo effect, which we in fact see in the data. Secondly, in this study, we were together with our patients for a whole week. Obviously, we talked with them and thus got to know them a little. By this interaction we might have influenced them; most likely we had a positive effect on them through this, as these are often patients who do not have a lot of social contacts in their daily life. By the end of the week, they might feel better just because of the daily routine with a purpose (the study) and having contact with others. There are two possible consequences of these interactions: First, the patients might start to like us and be hopeful for the study and our work, and therefore be more inclined to tell us that the treatment worked – a social desirability effect which increases the likelihood of finding a treatment effect but is a false positive. Secondly, as they spend time with us, they trust us more and report symptoms more honestly at post-treatment. We noticed more of their symptoms throughout the week, which would give a higher symptom rating at post-treatment, which is more correct, than the one we obtained at baseline. Hence, the symptom severity at baseline could be underestimated due to a lack of trust between patient and rater. This second notion would make it more difficult to find a treatment effect. This could partly have been solved by having different personnel for the treatment provision itself and the RCT data requisition.

5.4 Discussion on mechanisms of tDCS

As there were only sparse tDCS effects in all three papers included in this thesis, it is necessary to discuss the general mechanisms of tDCS and how these considerations might have affected our studies. There is a lot of critique on non-invasive brain stimulation and its effectiveness, both from researchers in the field and

other neuroscientists. To exemplify this critique there is a quote from Vincent Walsh (2013):

"*Based on the best available studies, from reputable laboratories, we don't really know where to put the electrodes, we don't know how robust is the idea that the effects are excitatory or inhibitory, we don't know what other behaviors are affected, we haven't tested the methods with real-world tasks and therefore don't know how they perform outside the lab, and we have no idea in healthy people if they continue to work after more than 2 or 3 repeated applications."*

While this is from 2013 and put somewhat exaggeratedly, it brings up several important points which will be discussed in the following paragraphs. The basic research on tDCS in this section is usually done in healthy controls, if not stated otherwise.

Early modeling of the electric field in tDCS showed that only about 10 % of the current (electric field of 0.22V/m) reaches the cortex with scalp current of 2 mA (Miranda, Lomarev, & Hallett, 2006; Vöröslakos et al., 2018), raising the question whether tDCS with such parameters would have an effect at all. Even though the modeling procedures have advanced substantially, it shows maximum values in the motor cortex of 0.2-0.5 V/m electric field strength (Miranda et al., 2018), which is in agreement with our own modeling where we found electric fields from 0.29 to 0.65 V/m at 2 mA tDCS. While the finding of little electricity reaching the brain caused quite a stir in the research community, it has been known for quite a while, and can be viewed as a mechanistic virtue of the method as well. It gives the opportunity to only modulate the firing threshold in neurons, not trigger action potential directly, as TMS does (Radman, Ramos, Brumberg, & Bikson, 2009).

In addition to a generally low electrical effect on the brain, the dose-response curve of tDCS is not well understood. Many studies ignore the fact that anode/cathode does not simply equate to excitatory/inhibitory at the current intensity delivered. It was earlier assumed that both 1mA and 2 mA stimulation have an excitatory anode and inhibitory cathode effect, but there is a growing body of

literature showing this might not be the case. Studies showed that 1 mA cathodal stimulation is inhibitory, while 2 mA is excitatory in the motor cortex (Batsikadze et al., 2013; Samani, Agboada, Jamil, Kuo, & Nitsche, 2019). Also Parkin et al. (2019) showed that the classical unilateral polarity (excitatory and inhibitory effects) of 1 mA does not hold when montage (e.g., bilateral) and intensity (e.g., 2 mA) are changed, in the motor cortex. Moreover, other papers have shown that the polarity effect of tDCS is not a given; in truth, direct current always produces bimodal polarization, this means anodal stimulation produces depolarization in the soma and hyperpolarization in the dendrite of a single neuron (Bikson et al., 2004), thereby enhancing synaptic processing (A. Rahman et al., 2013). A review concluded that the polarity effect is quite common in motor area investigations, but cannot be extended to cognitive studies (Jacobson et al., 2012).

Taken together, these findings indicate that in tDCS more is not always more, if one specifically wants to induce an excitatory AND inhibitory effect. As the hypofrontal/hypertemporal reversal model is based highly on the polarity of tDCS, this could mean that the tDCS montage to treat AVH could work more optimally with an intensity of 1 mA, to achieve the most polarity of excitation and inhibition over the DLPFC and TPC, respectively. To my knowledge there are no RCTs researching tDCS in AVH with 1 mA current. There is, however, a successful case report (Homan et al., 2011).

Most studies keep stimulation from 1 mA to 2 mA, for 10-30 minutes from 1-10 sessions. Protocols are mostly set up this way because we know it is safe (Antal et al., 2017) and due to historical development, but it is understudied whether this the most effective for the purpose of a particular outcome. As pointed out in the introduction, in the tDCS treatment of AVH RCTs vary in the number of sessions used (5-40) (Fröhlich et al., 2016; Lindenmayer et al., 2019), but meta-analyses have shown that higher frequency of sessions (two daily) and more sessions (at least ten) are superior to less to induce an effect (Cheng et al., 2020; J. Kim et al., 2019).

In addition, many tDCS studies show small effects, where it is hard to know if they have any real-life implications (Cheng et al., 2020; Minarik et al., 2016). Another issue is that tDCS research rarely includes control tasks and/or control sites in order to show that the effect is specific (Walsh, 2013). Clinical studies, including our own, are often underpowered, meaning that they include too few participants for drawing strong conclusions. In the case of tDCS treatment for AVH most of the largest studies have a sample size of around 50 participants (Koops et al., 2018; Mondino et al., 2018). Since they typically include a sham control group, this means around 25 participants actually received tDCS. A solution to this problem would be to pool datasets from different studies in order to get more power and conduct analysis on tDCS responders, which is something we plan to do with our study and Koops et al.

With the normal tDCS electrodes used here and in many other studies, with a size of 5x7cm^2, we cannot achieve very focal stimulation. A possible solution to this is a high definition tDCS montage, where four electrodes surround one (four cathodes are placed around one anode or vice versa) which focalizes current distribution and makes it possible to target brain areas more specifically (Knotkova, Nitsche, Bikson, & Woods, 2019). Higher focality could be achieved with the 5-point electrode set-up tDCS, which could improve the targeting of the DLPFC, the TPC, or Broca's area.

tDCS simulation shows a large degree of individual differences with respect to how much current is delivered to the cortex due to individual anatomy (Bikson, Rahman, & Datta, 2012). It was suggested that neuronavigation of tDCS might be a good tool to improve delivery of stimulation in different individuals (De Berker et al., 2013), and neuronavigation was recently used to predict individual doses of tDCS (Caulfield et al., 2020). However, this reduces the simplicity and affordability of the method greatly, as it requires MR imaging prior to tDCS. In addition to the sources of variability previously described, age and stage of the menstrual cycle may also affect tDCS performance (Thair, Holloway, Newport, & Smith, 2017).

So, what implications does the method discussion above have for this thesis? The montage with the anode over the left DLPFC and the cathode over the left TPC puts the electrodes relatively close together. That probably results in an activation peak between electrodes, that is, a single, larger electrical field, not two small ones directly under the electrodes; simulation of the electric field in paper II and III showed this. The normal component (going down into brain from surface) still goes straight into temporo-parietal lobe and frontal lobe, though. If this is the effective part of stimulation, the montage does not need to be changed to reduce AVH. Individual differences in skull and brain anatomy still need to be taken into account, especially in schizophrenia. For example, schizophrenia patients are often characterized by loss of gray matter (Glahn et al., 2008; Neckelmann et al., 2006). Loss of gray matter leads to larger ventricles filled with CSF and more CSF reduces stimulation, this could mean that there is less current reaching schizophrenia patients' brains than in healthy controls.

In summary, to treat AVH effectively with tDCS, at least 10 sessions are needed, preferably more. In order to overcome the problem of underpowered studies, multicenter studies could be conducted. Focality could be increased by using a high definition tDCS set-up instead of the traditional one and in order to get the best individual targeting of the tDCS current, neuronavigation can be used. Polarity might be superior with 1 mA, however in schizophrenia delivery of current to the brain could be more challenging than in healthy participants, which is a counter argument to decreasing stimulation intensity.

While there are still methodological issues to overcome, it is important to remind ourselves that non-invasive brain stimulation has been proven to work as treatment in certain disorders (Fregni et al., 2020), we just do not yet know exactly how and why it works. Taken together, the above points demonstrate that more basic research is needed to understand tDCS fully and in order to optimize treatment montages, both in AVH and other disorders.

5.4.1 Neuroimaging and tDCS

There is a large body of literature on tDCS with different MRI methods and to review this literature comprehensively would be beyond the scope of this thesis. I therefore decided to focus on research that aimed to examine the underlying mechanisms of tDCS with MRS in healthy participants. However, some of the issues raised in the next paragraphs (e.g., replication problems, underpowered studies, different tDCS parameters) also apply to other neuroimaging methods and neuroimaging/tDCS research in general.

In the motor cortex, Glx has been found to decrease after 1 mA cathodal stimulation, but Glx concentration did not change after anodal stimulation. Further, the authors reported that GABA concentrations decreased after anodal stimulation and cathodal stimulation (n = 11) (Stagg et al., 2009). Also, in the motor cortex, specifically the hand area, anodal 1.5 mA tDCS induced a significant reduction in GABA levels, while no changes in glutamine and glutamate measures were found (n = 35) (S. Kim, Stephenson, Morris, & Jackson, 2014) and 1 mA anodal stimulation caused a GABA decrease in 32 subjects (Patel et al., 2019). In the sensorimotor cortex at 1 mA, GABA levels were reduced after anodal tDCS but not after cathodal tDCS and no significant glutamate changes were reported (n = 48) (Antonenko et al., 2017).

In a small dataset (n = 9) a Glx increase under the anode was found in the right parietal cortex at 2 mA (Clark, Coffman, Trumbo, & Gasparovic, 2011; Hunter et al., 2015). Another study stimulating the DLPFC bilaterally (n = 17) found striatal Glx and prefrontal NAA levels to be elevated during 1 mA tDCS, but not after stimulation. No GABA level changes were found (Hone-Blanchet, Edden, & Fecteau, 2016). Cerebellar tDCS at 2 mA in 34 participants showed no changes in glutamate and GABA levels. (Jalali, Chowdhury, Wilson, Miall, & Galea, 2018). With 20 participants receiving anodal 2 mA tDCS over the left superior temporal gyrus no GABA, Glx or NAA level changes were found (Dwyer et al., 2018). Similarly, in 32

subjects no MRS alterations (Glx and moreover GABA) were found when the motor cortex was stimulated at 2 mA five times within 25 hours (Zappasodi et al., 2017).

From this short review of the literature on tDCS induced neurotransmitter changes in healthy participants it is evident that results vary greatly. For anodal stimulation in the motor cortex, most find GABA reduction (Antonenko et al., 2017; S. Kim et al., 2014; Patel et al., 2019; Stagg et al., 2009), but some find Glx decreases (Antonenko et al., 2017; S. Kim et al., 2014; Patel et al., 2019; Stagg et al., 2009) and some find no change in Glx (Antonenko et al., 2017; S. Kim et al., 2014; Zappasodi et al., 2017). Cathodal stimulation in the motor cortex was found to decrease both GABA and Glx levels in one study (Stagg et al., 2009), while there were no changes in another study in the sensory motor cortex (Antonenko et al., 2017). These studies vary in stimulation parameters such as montage and stimulation intensity and often comprise relatively small sample sizes. But even when looking at similar parameters (1mA in motor areas) the results vary, at least for Glx findings, indicating replication issues in the field. This holds for most neuroimaging research in the tDCS field. To uncover the mechanism of tDCS some papers call for a push for multimodal imaging techniques (Hunter, Coffman, Trumbo, & Clark, 2013; Tremblay et al., 2014). A consortium of different research groups, working towards bigger samples and a comprehensive mapping of parameters with multimodal imaging techniques, would be a solution to push the field forwards, as it is hard for single groups to achieve large sample sizes with these expensive and time-consuming techniques.

5.5 Limitations

An obvious limitation to paper I is that there is no control condition. The study was designed to try and help a young patient with acute, severe epilepsy symptoms as soon as possible and research design issues were of secondary relevance.

The tDCS treatment was generally well tolerated with little side effects, however in paper II the healthy participants reported relatively many side effects compared to other studies (Koops et al., 2018), supposedly due to the added stress of

MRI scanning at the same time. Which means that one needs to be aware of higher side effect profiles when tDCS and MRI are combined and that it does not necessarily reflect the tolerability of tDCS alone.

We only had a small patient sample in the RCT in paper III. The recruitment of patients was challenging, Bergen is a small city and the length of the study, in total seven days, made it difficult for some patients to travel to us. In some cases, we travelled to the patients' homestead to give tDCS treatment, but in those cases MR imaging was not possible. Another factor was a change in treatment policy in psychiatric clinics that coincided with the start of our RCT: Instead of being treated longer at the large psychiatric clinic where we would contact them through our project partners, the new policy meant that patients were sent more quickly to other smaller psychiatric clinics in the Bergen area as soon as they partly recovered. In addition, we were also looking for a quite narrow population of patients, which required medication resistant AVH and thus a substantial severity of illness but at the same time participants had to be functional enough to provide informed consent themselves and to undergo the RCTs assessment and treatment for seven days. The most severely affected patients were not able to undergo this extensive protocol, as evidenced by three dropouts out of 24 participants.

This implies that the tDCS treatment had a small effect on well-functioning, treatment-resistant hallucinators. One could speculate, that the tDCS treatment could have worked even better in more affected patients, which we were unable to include. It could also be the case that tDCS works in non-chronic patients, with short duration of illness, but not in patients with a long history of hearing voices, which is mostly whom we recruited in the study. It is also possible that due to cultural differences patient recruitment is more challenging in Norway than in other countries, as patients here have a high degree of self-determination such that they disagree to participate, even if it is recommended by the treating physician. This is however purely speculative.

There is a theory that tDCS works better when brain areas are already active, meaning that targeted areas need to be activated (e.g., by a task) for tDCS to have excitatory powers. This notion is called activity-selectivity (Bikson & Rahman, 2013). Since we administer tDCS without a task in the RCT, the effect could have been stronger with a task during stimulation. On the other hand, it is possible that when patients hallucinate during tDCS, the increased activity in their language areas might serve as activity-selectivity and facilitate the treatment effect. However, it was not controlled for in the RCT, whether patients were hallucinating during tDCS treatment. This means that our study treated AVH as a "trait" variable as opposed to a "state" variable. Hugdahl (2015) distinguishes between whether AVH are studied as a general trait by, for instance, clinical interviews or whether AVH are studied as a state, in the moment they are experienced (e.g., as indicated by a button press). It might be argued that a state approach could have benefitted this study.

Hypothetically, patients could only be stimulated while hearing voices, but that is just not realistic as there are very few patients hallucinating all the time or in a manner that can be planned in coherence with tDCS sessions. Another possibility would have been that patients either indicated during the daily tDCS sessions, if they had AVH, or at least were asked about it shortly after each session. However, this would have made the already very extensive assessment only more demanding.

Nevertheless, we tried to address this issue by setting up a separate study (not detailed in this thesis) which involved participants undergoing tDCS (20 min, 2 mA) in the MR-scanner. During tDCS, they indicated via button press how often and for how long they experienced AHV. Only patients that hallucinated frequently enough to expect hallucinations in a 20 min time window were invited and underwent the combined tDCS/fMRI/experience sampling procedure twice, once while receiving real tDCS and once while receiving sham tDCS. The hypothesis was that the AVH would be reduced during the real tDCS compared to sham and that it would show "in real time" by reduced button presses. However, at this point we have too few participants and hallucination periods to carry out meaningful statistics for this study. While there is empirical support for the activity-selectivity notion, we did not observe

tDCS effects in paper II, where participants performed the dichotic listening task during stimulation. This would argue against the activity-selectivity theory.

Overall limitations for all three studies are low sample sizes, in line with previous studies using tDCS. It is desirable for future studies to acquire larger sample sizes.

6. Conclusion and future research

Taken together, the thesis provided the following answers to the research questions set out in the introduction:

1) Can tDCS reduce auditory hallucinations?

In the studied sample, tDCS did relieve auditory hallucinations, but the placebo effect and real tDCS were difficult to distinguish and the AVH reduction was only seen in self report measures, and not in interviews performed by examiners.

2) Is there supporting evidence for the hypofrontal/hypertemporal reversal model of the tDCS treatment?

Neither paper II nor III showed results which would corroborate the idea that tDCS with the DLPFC and TPC montage compensates the hypofrontal/hypertemporal activity pattern. The underlying mechanisms of tDCS in general, but also this specific tDCS montage for AVH, need to be further explored; a reasonable starting point might be Broca's area.

3) What are the neurochemical and functional changes in the stimulated brain regions of tDCS treatment?

Very few neurochemical and functional activity changes were found in connection with tDCS - at least with the parameters, montage, and healthy participants/patients used in the present studies. In the patient data, there were also no structural or functional connectivity findings in the regions of interest, the DLPFC and TPC. The hypothesized brain activity increase under the anode, with corresponding increase in Glx and/or decrease in GABA was not found. Neither did we find changes in the region underneath the cathode. Our findings suggest that the hypofrontal/hypertemporal reversal model of how tDCS treatment reduces AVH may need to be revised.

4) Does tDCS relieve symptoms in POLG mutation specific epilepsy?

In the presented case, tDCS did not relieve epilepsy, as spike activity was not reduced, nor were symptoms: muscular jerking was not reduced.

Our data imply that future research needs to verify that tDCS has an effect beyond the placebo effect in AVH. If the effect size of the presented study turns out to be realistic, then we only rely on the placebo effect. Though placebo can be powerful, tDCS itself would not be effective. As described, tDCS did only induce small significant changes or treatment effects on AVH in our study, but we see in the literature and from individual cases in our RCT that it can have beneficial effects. To this end, the tDCS research field needs to combine forces to find out under which parameters the method is effective. That is, montages, session length, intensity (1 or 2 mA), number of treatment sessions, electrode sizes and electrode shapes and so forth.

Gaining a better understanding of the mechanisms that underlie tDCS treatment of AVH (and other disorders) is a stepping stone to improve the treatment itself. To achieve this, more basic research on mechanisms is needed, preferably in the multimodal manner of the 2nd and 3rd paper described in this thesis. In patient groups, large RCTs need to be conducted, where it is possible to determine subgroups of patients which can have beneficial effects of tDCS (tDCS responders), related to severeness and length of illness and auditory verbal hallucinations, age, gender, nicotine addiction, medication interactions, and other factors.

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Case Report

No effect of electrical transcranial direct current stimulation adjunct treatment for epilepsia partialis continua in POLG disease

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ABSTRACT

We report a 15-year-old female with POLG-related mitochondrial disease who developed severe multifocal epilepsia partialis continua, unresponsive to standard anti seizure drug treatment and general anesthesia. Based on an earlier case report, we treated her focal seizures that affected her right upper limb with 20-min sessions of transcranial direct current stimulation (tDCS) at an intensity of 2 mA on each of five consecutive days. The cathode was placed over the left primary motor cortex, the anode over the contralateral orbitofrontal cortex. Surface electromyography (EMG) were recorded 20 min before, 20 min during, and 20 min after four of five tDCS sessions to measure its effect on the muscle jerks. The electroencephalography (EEG) was recorded before and after tDCS to measure the frequency of spikes. Our results showed no statistically or clinically significant reduction of seizures or epileptiform activity using EEG and EMG, with this treatment protocol. To our knowledge, this is only the second time that adjunct tDCS treatment of epileptic seizures has been tried in POLG-related mitochondrial disease. Taken together with the positive findings from the earlier case report, the present study highlights that more data are needed to determine if, and under which parameters, the treatment is effective.

1. Introduction

Mitochondrial diseases are a group of genetic disorders affecting about one in 5000 people [1]. The symptoms are diverse but since mitochondria produce energy for body tissues through production of adenosine triphosphate (ATP), organs with high energy consumption, such as the brain, are often affected. For example, as many as 35% to 60% of people with mitochondrial disease develop seizures [1]. In POLG-related mitochondrial disease, a genetic mutation interferes with a catalytic subunit of the mitochondrial DNA polymerase gamma, which replicates mitochondrial DNA [2], leading to depleted mitochondrial DNA [3]. Once the resulting neuronal energy failure reaches a critical point, neuronal death ensues, causes atrophy and potentially acts as the trigger for epilepsy that in turn increases neuronal loss [4]. A study found mitochondrial dysfunction in one third of patients with epilepsy that underwent metabolic testing [5], emphasizing that drug-resistant seizures are a frequent problem in mitochondrial disease, and that new treatments need to be developed. In a previous case report, focal seizures in a patient with POLG-related mitochondrial disease ceased after two weeks of transcranial direct current stimulation (tDCS) [6]. Since these seizures are often refractory to medical treatment and the technique is non-invasive, we tested tDCS using similar parameters as in Ng et al. [6] in a patient with POLG-related mitochondrial disease and drug-resistant multifocal epilepsy.

1.1. Case report

This 15-year-old female was apparently healthy until the first admission followed two consecutive generalized tonic–clonic seizures. Prior to the seizures, she had experienced nausea, headache, reduced vision and paraesthesia in both upper limbs. She was intubated during helicopter transfer to hospital due to reduced consciousness. Following admission, she regained consciousness, but developed continuous jerking of her right arm. EEG showed ongoing epileptiform discharges over the right occipital region (Fig. 1A) that later involved most of the

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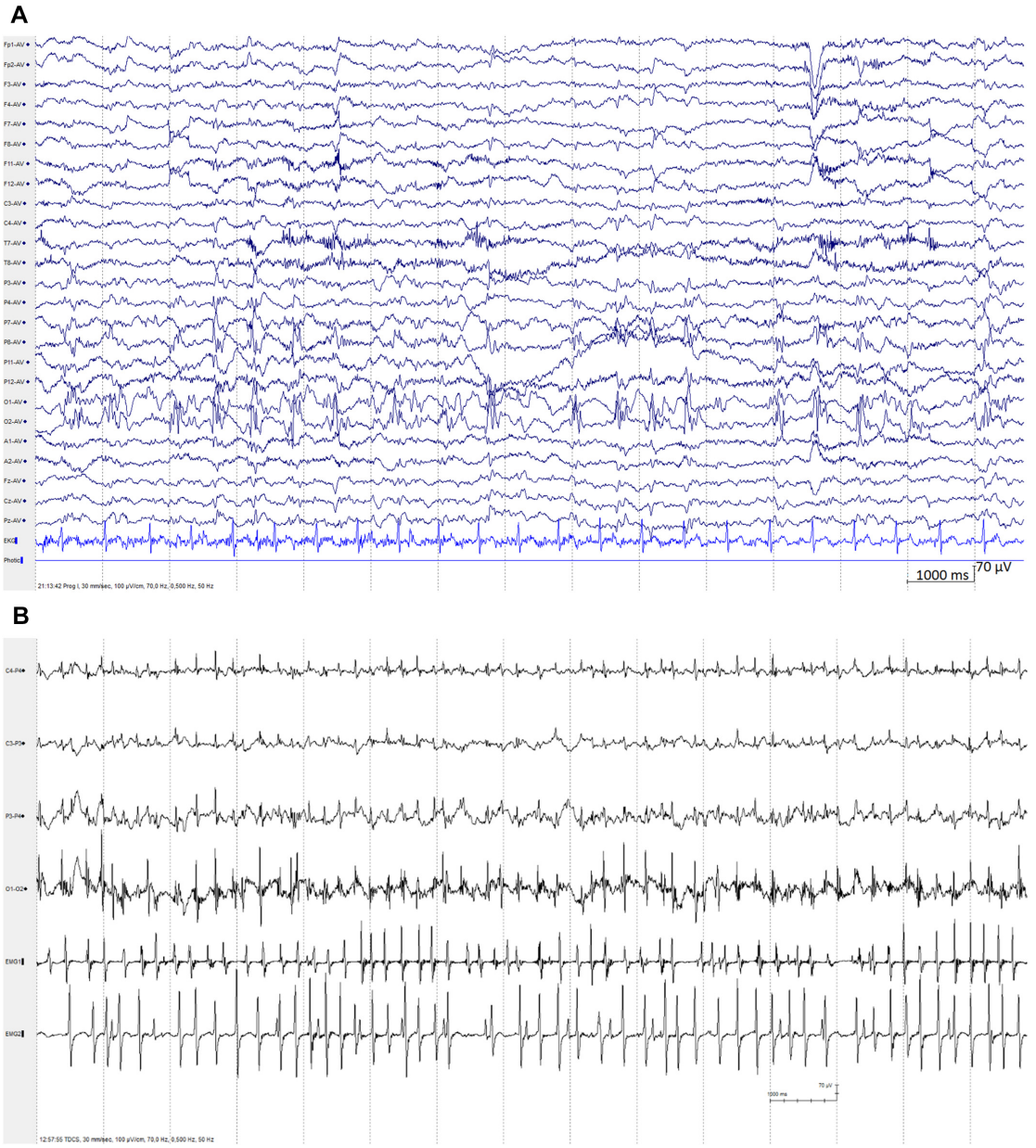

Fig. 1. POLG disease visualized through EEG examples. Panel A) EEG sample from the patient from an early clinical recording, showing almost continuous 2 Hz polyspike-and-slow waves mainly over the right parieto-occipital region. Panel B) Continuous EEG recording from the tDCS experiment showing channels (from top to bottom) C4, C3, P3, O1 and EMG1 and EMG2 being the right hand and left trapezius, respectively.

right cerebral hemisphere, and because of persisting uncontrolled epileptic activity she was loaded with phosphenytoin before using anesthesia with propofol and ketamine at relevant clinical dosages to provide effective serum levels, as well as lowering her core body temperature to 33 °C in accordance with the Norwegian treatment guidelines [7]. The clinical presentation with status epilepticus involving an occipital lobe focus prompted investigation for *POLG* mutation, which was subsequently confirmed through DNA sequencing analysis showing a homozygous genotype c.2243G>C.

Following two episodes of propofol anesthesia and achieving burst suppression, she regained consciousness and her epilepsy was then treated with phenobarbital and oxcarbazepine while withdrawing phenytoin. After stabilization, the patient was discharged with ongoing medication treatment. She was readmitted a second and third time

with headache and visual disturbances that quickly morphed into generalized tonic–clonic seizures, followed by focal motor status epilepticus, both episodes treated with anesthesia and hypothermia. On the third occasion, her MRI showed new changes in both occipital regions. During the second prolonged admission, she still had jerking of her right arm despite maintaining phenytoin, levetiracetam, oxcarbazepine, topiramate and clobazam at therapeutic doses. At the point where tDCS treatment was instituted, the patient had a multifocal seizures with multiple semiologies (Fig. 1A and B) including a multifocal, asynchronous myoclonus, that was dominant and most debilitating in the right hand. We thus targeted the left primary motor cortex with tDCS, as the myoclonus activity most likely arose from that area, with the goal to relieve pain and disability.

1.2. Methods of tDCS and EEG

The use of tDCS was discussed with the local ethical committee who considered it a form of supplementary experimental treatment whose purpose was to provide care for an individual, and for which the caring physician could take responsibility without obtaining the committees' approval. Verbal consent was obtained from the parents and treatment was reported in the patient's medical journal. tDCS was applied for 20 min at 2 mA on each of five consecutive days with a DC-Stimulator PLUS (neuroConn, Ilmenau, Germany) through 5 × 7 cm rubber electrodes with saline soaked sponges giving a current density of 0.057 mA/cm^2. The patient displayed continuous jerking in the right hand muscles and left shoulder muscles. To reduce the jerking of the

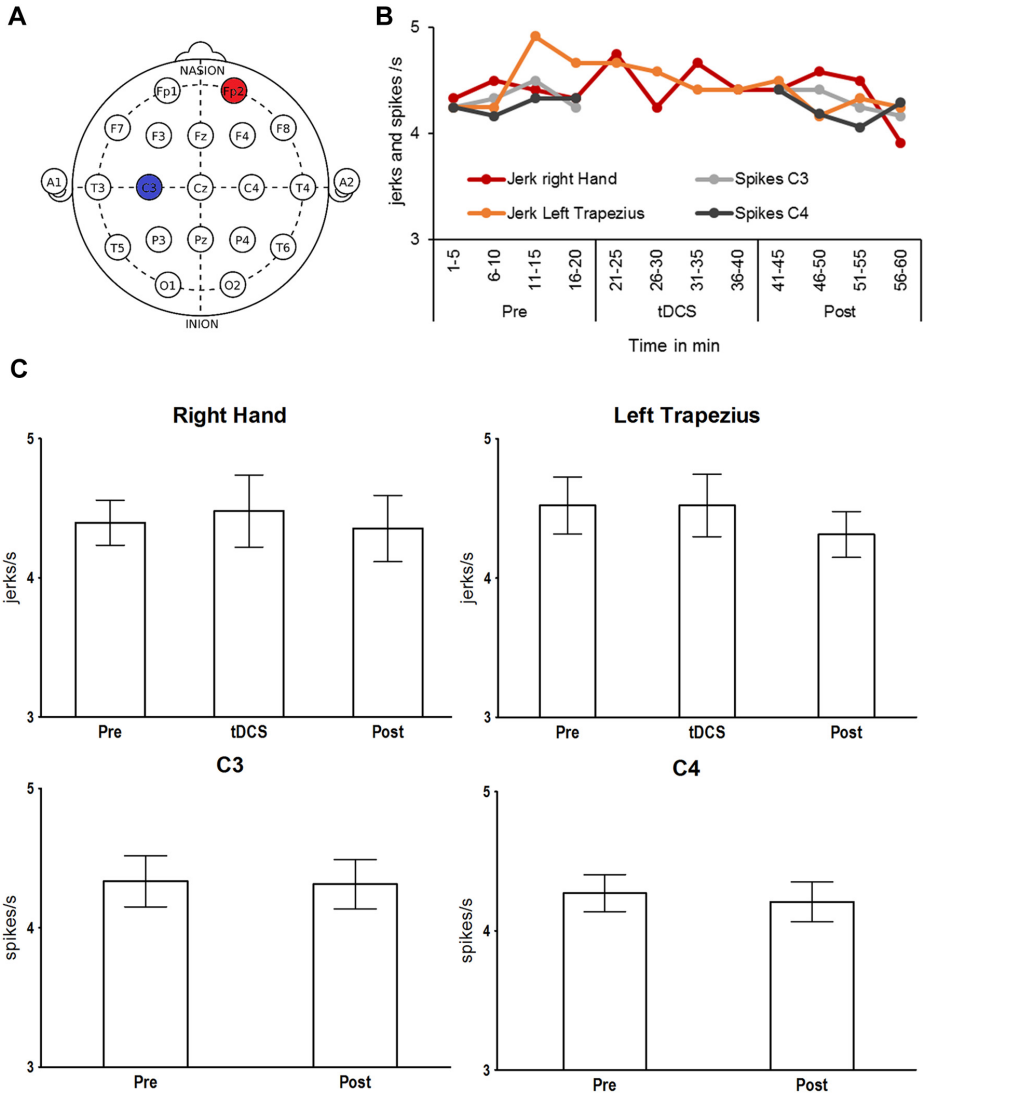

Fig. 2. tDCS montage and results. Panel A) Placement of anode at Fp2 (red) and cathode at C3 (blue) within the international 10/20 system. Panel B) Means of spikes/jerks per second across all four days. Time in minutes. Panel C) Spikes/jerks per second and 95% confidence intervals before, during, and after treatment.

right hand, the cathode was placed over the contralateral left primary motor cortex at approximately C3 of the 10–20 EEG system (see Fig. 2A). The rationale was that cathodal stimulation has been shown to reduce cortical excitability in the brain area underneath the electrode and hence might reduce epileptic activity causing the myoclonus [8]. The anode was placed on the right orbitofrontal cortex (approximately Fp2). By placing the electrode on the contralateral side, the electric field between anode and cathode crosses the midline and was hoped to affect the motor cortex most effectively. Since the anode is active and expected to increase cortical excitability, a better setup would have included an extra-large anode that would effectively reduce the current strength. However, as the tDCS treatment was issued at short notice, we did not have large electrodes available at the time. We chose the orbitofrontal region, because it is often used as a control site in tDCS experiments [9] and because it was not particularly affected by epilepsy. Indeed, we did not observe a worsening in the EEG in this region after the treatment. The tDCS setup was used in accordance with safety guidelines [10,11].

Initial EEG recordings and seizure monitoring during status epilepticus were done with continuous 25 channel clinical EEG and scored visually by experienced neurophysiologists. With the cathode placed over the left primary motor cortex, we looked for improvement particularly in the right hand. Continuous EEG was measured from C3 and C4 (right motor cortex as control) for 20 min before and 20 min after tDCS, from a clinical EEG setup following the 10/20 system with 6 + 2 (F3, F4, P3, P4, O1, O2) electrodes and video monitoring of the patient. EMG data from the right hand and left trapezius was acquired continuously for 20 min before tDCS, during 20 min tDCS, and 20 min after tDCS. EEG data was not interpretable during tDCS due to amplifier blocking. EMG and EEG data were recorded on four out of five days.

Three separate raters, two neurophysiologists (TE, HKO) and the tDCS clinician (LM), counted the frequency of spikes (EEG) and muscle jerks (EMG) drawn from multiple random samples. Specifically, the data were binned into 12 five-minute segments. Then, each rater picked randomly ten, artifact-free one-second periods from each five-minute segment on all four days and determined the mean number of EEG spikes and EMG jerks per second (Hz) for all four measurements (C3, C4, right hand, left trapezius). Subsequently, means were calculated across raters (see Fig. 2B) and EEG data was subjected to paired sample *t*-tests and non-parametric Wilcoxon tests, comparing spikes before and after tDCS. The means for EMG data were subjected to an ANOVA with the repeated measures variable *Time* (before, during after tDCS) and a non-parametric Friedman test. Non-parametric Friedman and Wilcoxon tests were included because not all variables met the normal distribution criterion necessary for *t*-tests and ANOVAs — due to the limited range of values for spikes/jerks per second. At the same time, non-parametric tests are sometimes not sensitive enough to pick up small effects. In the interest of comprehensiveness, we thus decided to report findings from both ANOVA/Friedman and paired sample *t*-tests/Wilcoxon tests. We also compared the pre-tDCS data on day one (baseline) to the post-tDCS data on day five using *t*- and Wilcoxon tests, assuming that the treatment effect should be strongest between these measurement points.

2. Results

Fig. 2C shows the average frequency of epileptic spikes and jerks in the right hand and left shoulder during treatment. According to *t*-tests/Wilcoxon tests for EEG data and the ANOVAs/Friedman tests for EMG data, there were no significant differences in the means across all raters in C3 or C4 spikes (all $ts_{(15)} \leq 0.613$, all $ps \geq 0.549$; all $\chi^2 s_{(1)} \leq 0.091$, all $ps \geq 0.763$) as well as jerks in the right hand and left shoulder (all $Fs_{(2,30)} \leq 1.74$, all $ps \geq 0.192$; all $Zs \geq 0.642$, all $ps \geq 0.521$). The mean spikes and jerks across all raters for pre-tDCS on day one (baseline) versus post-tDCS on day five were for the right hand 4.58 ± 0.32 and 4.42 ± 0.57, left trapezius 4.58 ± 0.32 and 4.08 ± 0.42 jerks/s, C3 4.50 ± 0.43 and 4.25 ± 0.32 and C4 4.25 ± 0.32 and 4.13 ± 0.17 spikes/s, respectively. None of these changes were significant (all $ts \leq 1.57$, all $ps \geq 0.215$; all $Zs \leq 1.34$, all $ps \geq 0.180$).

TDCS treatment was given in March 2018. The stimulation itself was well tolerated. The patient only reported short-term skin irritation from the net holding the electrodes in place. Four months after receiving tDCS, the patient was discharged from the hospital, still with upper limb jerking, but was readmitted in December 2018 and died due to a super-refractory status epilepticus.

3. Discussion

Neither spike nor jerk frequency changed over the course of five tDCS sessions (between before, during, and after tDCS) or when comparing baseline spike/jerk rates from day one to after treatment on day five. We therefore conclude that – in this case study – tDCS did not have a beneficial treatment effect on treatment-resistant refractory epilepsia partialis continua in POLG-related mitochondrial disease. Hence, our results are inconsistent with those of Ng et al. [6], who found that seizures stopped completely in a similar case study.

There are several differences between the two case studies that could explain the different outcomes: Ng et al. [6] placed the cathode over the right temporo-parietal–occipital junction (P4/T6), while in our study it was over the left primary motor cortex. Ng et al. provided tDCS treatment twice, once for three days and once for 14 days, while we provided tDCS treatment once for five days. However, the treatment in our case was stopped before the completion of 14 days because there was no sign of improvement and due to technical reasons/staff availability. Moreover, while the patients appeared to have similar seizure frequency their genotypes were different; the patient reported by Ng and colleagues was homozygous for the c.1399G>A whereas our patient was homozygous for the c.2243G>C genotype. Both patients were also on multiple, but different anticonvulsant regimens, raising the possibility that competing mechanisms modulated response to tDCS. Lastly, our case was severe, so by the time we started the intervention the seizures may have become refractory to both medication and tDCS treatment. We cannot rule out that cathodal stimulation elsewhere (e.g., over the right occipital region) might have yielded a better treatment response, perhaps, at an earlier stage of the disease. However, while the patient had a multifocal epilepsy with multiple semiologies, we specifically targeted the left motor cortex to reduce the myoclonic jerking of the right hand that the patient found very debilitating. Similarly, we cannot rule out that stimulating for more than five days would have worked better.

According to guidelines published by a European expert consortium in 2017, and several reviews, it is not yet possible to draw conclusions regarding the efficacy of tDCS in any kind of epilepsy, even though there are some promising results [12–15]. Similarly, it remains unclear whether transcranial magnetic stimulation (TMS), another type of non-invasive brain stimulation, is an effective treatment of epilepsy [16–18], although there are some positive findings for epilepsia partialis continua [19]. Even less is known about how these non-invasive brain stimulation techniques will affect patients with mitochondrial diseases. However, given that refractory epilepsy appears to be common in these diseases [5], finding novel treatments is highly relevant. To our knowledge, this is only the second documented attempt to use tDCS in mitochondrial disease. With one positive and one negative result, it is too early to say whether tDCS will find a place in the treatment of mitochondrial epilepsy, but during the early stages of any new treatment, *all* findings, negative or positive, need to be published to obtain a clearer overall picture. This is particularly relevant in this case, where almost nothing is known about the efficacy of tDCS for epilepsy in patients with mitochondrial diseases. Further, because the condition is so rare, it is difficult to realize randomized controlled trials with decent sample sizes and that could control for potential placebo effects. A final reason for why we deem it important to report this negative finding is – despite its limited contribution to the literature – that there is growing

awareness of reporting bias and replication issues in the scientific community and with it a growing recognition of the relevance of negative findings. We hope that our findings contribute to a growing body of literature and encourage other scientists to provide larger samples and proper clinical trials.

Author contribution

Conception and design of the study: LAB, GV and MH. Acquisition of data: LM, IK, TE, HKO, MH and LAB. Analysis and interpretation of data: LM, IK, TE, HKO and MH. Drafting the manuscript or figures: All authors. Critical review and revision: All authors.

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Ethical statement

The work described has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declaration of competing interest

None.

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RESEARCH REPORT

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A multimodal study of the effects of tDCS on dorsolateral prefrontal and temporo-parietal areas during dichotic listening

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Abstract

The underlying neural mechanisms of transcranial direct current stimulation (tDCS), especially beyond the primary motor cortex, remain unclear. Several studies examined tDCS effects on *either* functional activity, neurotransmitters *or* behavior but few investigated those aspects together to reveal how the brain responds to tDCS. The objective is to elucidate the underlying mechanisms of tDCS using a multimodal approach that extends from behavioral to neurotransmitter levels of explanation. Thirty-two healthy participants performed an auditory dichotic listening task at two visits, one session with sham and one session with real tDCS (2 mA) while simultaneously undergoing functional magnetic resonance imaging (fMRI). The anode and cathode were placed over the left temporo-parietal cortex (TPC) and dorsolateral prefrontal cortex, respectively. Before and after simultaneous dichotic listening/fMRI/tDCS, combined glutamate and glutamine (Glx) and myo-inositol levels were assessed in the stimulated areas. While fMRI and dichotic listening showed expected functional activity and behavioral effects, neither method demonstrated differences between real and sham stimulation. Glx only showed a statistical trend towards higher levels after real tDCS in both stimulated brain areas. There were no significant correlations between behavior and Glx. Despite a reasonable sample size, electrical field strength, and replication of behavioral and functional activity results, tDCS had little to no effect on dichotic listening, Glx, and functional activity. The study emphasizes that findings about the underlying neural mechanisms of the primary motor cortex cannot simply be generalized to other brain areas. Particularly, the TPC might be less sensitive to tDCS. Moreover, the study demonstrates the general feasibility of multimodal approaches.

Abbreviations: DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; GABA, γ-aminobutyric acid; Glx, glutamine and glutamate; MR, magnetic resonance; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; PRESS, point resolved spectroscopy sequence; SNR, signal to noise ratio; tDCS, transcranial direct current stimulation; TE, echo time; TPC, temporo-parietal cortex; TR, time to repeat.

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KEYWORDS

electric field simulation, functional magnetic resonance imaging, magnetic resonance spectroscopy, transcranial direct current stimulation

1 | INTRODUCTION

Despite substantial progress, the underlying neural mechanisms of transcranial direct current stimulation (tDCS) are still not well understood. In humans, the effects of tDCS are typically studied with respect to behavior (Ditye, Jacobson, Walsh, & Lavidor, 2012; Westwood, Olson, Miall, Nappo, & Romani, 2017), brain activity (assessed with functional magnetic resonance imaging, fMRI) (Antal et al., 2012) and neurotransmitters/neurometabolites (Kim, Stephenson, Morris, & Jackson, 2014; Stagg et al., 2009). For instance, several studies investigated tDCS effects on gamma-aminobutyric acid (GABA) and glutamate, the main inhibitory and excitatory neurotransmitters, respectively. Some reported an increase of Glx (glutamate + glutamine) levels after anodal stimulation (Clark, Coffman, Trumbo, & Gasparovic, 2011; Hunter et al., 2015) and a Glx decrease after cathodal stimulation (Stagg et al., 2009). However, there are also null findings on glutamate or Glx (Antonenko et al., 2017; Dwyer et al., 2018; Kim et al., 2014). Another study found a significant increase in myo-inositol under the anode (Rango et al., 2008). Myo-inositol is a carbocyclic sugar, derived from glucose and involved in signal transmission in the brain. Others have examined tDCS effects on fMRI measures in motor or cognitive tasks. For example, Antal, Polania, Schmidt-Samoa, Dechent, & Paulus (2011) found a significant decrease of the blood oxygen level-dependent signal in the supplementary motor cortex when participants performed a finger-tapping task and were stimulated with anodal tDCS over the primary motor cortex. Weber, Messing, Rao, Detre, & Thompson-Schill (2014) reported changes in brain connectivity, as assessed with fMRI, due to tDCS during a risk assessment paradigm.

However, few studies looked at tDCS effects on behavior, brain activity and neurotransmitters *together*, although such a multimodal, neuroscientific approach may be more promising to reveal the associations between different aspects of brain functioning (Hunter, Coffman, Trumbo, & Clark, 2013; Tremblay et al., 2014). For instance, participants in Antonenko et al. (2017) received tDCS over the sensorimotor cortex during resting-state fMRI and GABA levels were measured before and after. The results showed reduced GABA levels after anodal tDCS compared to sham. Another study by the same group found that both anodal and cathodal tDCS decreased GABA levels and increased sensorimotor network connectivity and the tDCS induced changes in GABA levels correlated with the simulation of the tDCS electric field strength (Antonenko et al., 2019).

Studies investigating the underlying mechanisms of tDCS often focus on stimulation of the primary sensory/motor cortex (Antal et al., 2011, 2012; Antonenko et al., 2019; Kim et al., 2014; Stagg et al., 2009). We aimed to extend that work and examined the left dorsolateral prefrontal cortex (DLPFC) and left temporo-parietal cortex (TPC) with respect to tDCS effects on behavior, neurotransmitter levels and functional brain activity—within the same study. We chose those two brain areas to test a model that seeks to explain auditory hallucinations in patients with schizophrenia by assuming that *hyper*active temporo-parietal areas give rise to auditory hallucinations and *hypo*active prefrontal areas limit an individual's capacity to control the hallucinations (Hugdahl, 2009, 2015). Tentative evidence for the model comes from treatment studies where anodal tDCS over the prefrontal areas (with a supposedly excitatory effect) and cathodal stimulation of temporal areas (with a supposedly inhibitory effect) reduced hallucinations in patients with schizophrenia (Brunelin et al., 2012).

We aimed to test the model in healthy individuals using the Bergen dichotic listening task, in which simple speech sounds are presented to the left and right ear (Hugdahl et al., 2009). It was chosen because it is a reliable and well-established behavioral paradigm that involves both the DLPFC and the TPC, as revealed by functional neuroimaging (Westerhausen, Kompus, & Hugdahl, 2014). Behaviorally, it produces a right ear advantage that is modulated by participants' attention (Hugdahl, 2004). This right ear advantage and attentional modulation are typically reduced in schizophrenia patients (Hugdahl et al., 2013; Ocklenburg, Westerhausen, Hirnstein, & Hugdahl, 2013). Thus, by placing the excitatory anode over the TPC and the inhibitory cathode over the DLPFC in healthy individuals, we intended to "mimic" the reduced right ear advantage/generally fewer correct responses and the corresponding hypertemporal/hypofrontal activity pattern in schizophrenia patients as a test for the model.

More specifically, we hypothesized that excitatory, anodal stimulation of the left TPC and inhibitory, cathodal stimulation of the left DLPFC would lead to higher and lower levels of Glx, respectively. Functional brain activity would increase in the left TPC due to anodal excitation and Glx increase, and decrease in the left DLPFC, during tDCS as compared to sham. The right ear advantage would be reduced due to interference caused by increased Glx levels and reduced Glx levels in the left TPC and DLPFC, respectively. Based on findings showing Glx increase under the anode and decrease under the cathode (Clark et al., 2011; Stagg et al., 2009), we predicted that Glx in the left DLPFC

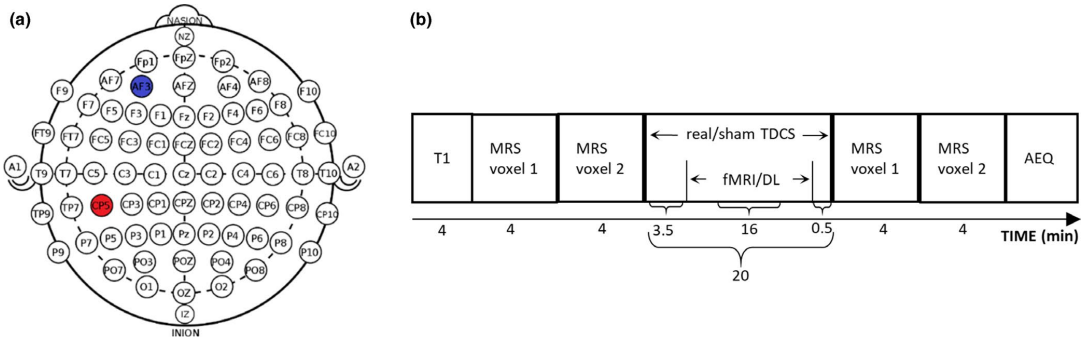

FIGURE 1 Electrode Montage and Experimental setup of one visit. Panel a) The cathode (blue) was placed over AF3 and the anode (red) over CP5. Panel b) Participants completed a dichotic listening task while undergoing simultaneous tDCS/fMRI. Before and afterwards, MR spectroscopy was performed in both stimulated areas. T1 was a structural scan that was used for modelling the electric field. At the end, participants completed an adverse effects questionnaire. Each participant visited twice, receiving once sham and once real tDCS.

(cathode) should be correlated negatively with a stronger, more focal electric field. In turn, Glx concentrations in the left TPC (anode) should be correlated positively with a stronger and focal electric field.

2 | METHODS

2.1 | Participants

Initially, 38 participants were recruited via flyers and word-of-mouth at the Haukeland University Hospital, Bergen, Norway. Exclusion criteria were past/present neurological or psychological disorders, head trauma, metallic implants, epilepsy in first degree relatives, pregnancy, claustrophobia, acute consumption of drugs or alcohol at time of testing, and severe skin diseases in the area of the electrode placement. Six participants had to be removed from the analysis due to incomplete data ($n = 1$), insufficient magnetic resonance spectroscopy (MRS) quality, ($n = 4$) and incorrect stimulation protocol ($n = 1$).

The mean age of the remaining 32 participants (18 male/14 female) was 26 ± 4.8 years (range = 20–39). Participants had a mean of 16 ± 2 years of education. All participants were screened for hearing deficits and could detect frequencies between 250 and 3,000 Hz at an intensity of <20 dB. Further, none of the participants had an interaural acuity difference of more than 10 dB (see also Hirnstein, Hugdahl, & Hausmann, 2014; Hirnstein, Westerhausen, Korsnes, & Hugdahl, 2013). All participants gave written informed consent in accordance with the Declaration of Helsinki and were reimbursed for their participation. The study was approved by the Regional Committee for Medical Research Ethics in Western Norway (REK Vest) # 2013/2342.

2.2 | Procedure

The dichotic listening paradigm was carried out during fMRI to assess tDCS effects on functional brain activity. Moreover, immediately before and after simultaneous tDCS/fMRI/dichotic listening, participants underwent MRS to measure glutamate. Finally, we took inter-individual differences in electric field parameters into account through simulation of tDCS effects based on structural MR scans.

A reporting checklist with an overview of the study's design, following the recommendations by Buch et al. (2017), is provided in the Appendix S1. Participants were tested twice, once with real and once with sham stimulation in a counter-balanced double-blind design. Fifteen participants received real, 17 sham tDCS in the first session. The real and sham tDCS sessions were separated by 8.4 ± 3.2 days on average (range: 4–16 days).

Only at the first session, participants provided informed consent and completed the hearing test as well as the dichotic listening task practice trials. In both sessions, they completed questionnaires concerning tDCS and MR safety, and electrode positions for tDCS were located with EEG caps (EASYCAP GmbH), based on the 10/20 system (Figure 1a), before entering the MR scanner. Rectangular, MR compatible tDCS electrodes made of rubber (5 cm × 7 cm) were used. The cathode and anode were placed over AF3 (left DLPFC) and CP5 (left TPC), respectively. Electrodes were coated with conductive paste Ten20 (Weaver and Company) and a 9 mg/ml NaCl solution to decrease impedance and attached to the scalp via a rubber band. Impedance was kept below 14.2 kΩ, which was tested outside the MR scanner.

After the impedance check, participants entered the GE 750 3T Scanner. In both sessions, the MR sequences

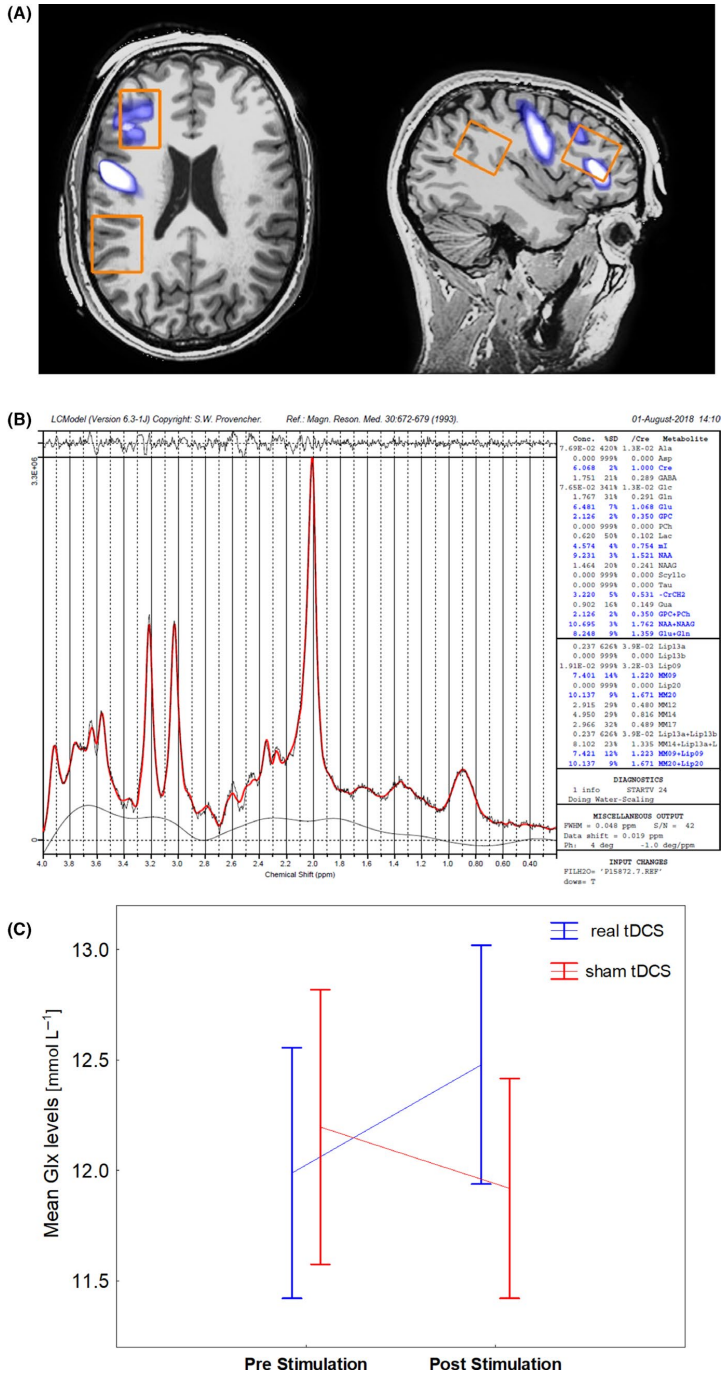

FIGURE 2 MR spectroscopy setup and results. Panel a) Voxel placement during MRS acquisition of the DLPC and TPC (sagittal and axial view) from one participant (in orange) and the simulated peak activation, threshold at 0.48 V/m for the illustration, as a group average (in blue). Panel b) Typical successfully acquired MRS spectrum as given by LCModel. The black line denotes the measured data, the red line the model. Concentration estimates for the different neurotransmitters are given in the right-hand box. Panel c) Trend towards increased Glx levels after real tDCS as compared to sham tDCS. Vertical bars denote 95% confidence intervals

were completed in the order as described below (see also Figure 1b). For all details regarding MR acquisition, quality control and hardware/software, please see Appendix S1.

2.2.1 | Structural MRI

After a localizer sequence, participants underwent a structural anatomical image 3D T1-weighted fast-spoiled gradient

sequence. The structural MR scan was carried out first for placing the voxels for the subsequent MRS and allowed electric field parameter simulations.

2.2.2 | MR spectroscopy

The structural scan was followed by two single-voxel point resolved spectroscopy (PRESS) sequences. Two voxels were placed, based on the T1 images, in the left DLPFC and the left TPC (Figure 2a). After the simultaneous tDCS/fMRI/dichotic listening sequence, MRS was performed again in both voxels. The voxel order was identical before and after the simultaneous tDCS/fMRI/dichotic listening sequence. In the second session, voxel order was reversed. Seventeen participants began with the left TPC, and 15 participants began with left DLPFC in the first session. The order was randomized, meaning, seven participants who began with the left TPC started with real and 10 started with sham. For the DLPFC, eight participants started with real and seven participants started with sham.

2.2.3 | tDCS

After MRS, the electrode cables were connected to the inner box and stimulation began. Codes were used to ensure double-blinding. tDCS lasted 20 min (+30 s ramp up and 30 s ramp down) at 2 mA (current density = 0.057 mA/cm) from an MR compatible DC-Stimulator Plus (neuroConn GmbH). Sham tDCS was delivered for 40 s, followed by very weak pulses of 110 μA lasting 15 ms, provided every 550 ms as an impedance check.

2.2.4 | Dichotic listening fMRI paradigm

During tDCS, participants completed a dichotic listening paradigm that was adapted to fMRI. It lasted 16 min and began 3.5 min after tDCS had started to ensure the left TPC and DLPFC had already been stimulated for a while (Figure 1b). In each dichotic listening trial, two out of six different syllables (/ba/,/da/,/ga/,/pa/,/ta/ and/ka/) are presented simultaneously, one to each ear. For example,/ba/ to the left ear and/ka/ to the right ear. Homonyms (e.g., /ba/-/ba/) were not included, leaving 30 possible syllable combinations. Participants completed these 30 trials twice, in three different conditions: In the non-forced condition, participants were instructed to verbally report the syllable they heard best and most clearly. In the forced-left and forced-right condition, they were instructed to specifically report the stimulus from the left and right ear, respectively. Verbal responses were scored and recorded during scanning as a measure of behavioral data.

The dichotic listening paradigm was carried out in a block design during fMRI acquisition, using an echo-planar imaging sequence. The paradigm had 270 volumes in total, distributed across 25 blocks (seven resting blocks + six non-forced + six forced-right + six forced-left). The block order was pseudo-randomized. Each block consisted of 10 trials, resulting in 180 dichotic listening volumes/trials and 70 resting volumes (Hugdahl & Andersson, 1986; Hugdahl et al., 2009; Thomsen, Rimol, Ersland, & Hugdahl, 2004). A silent gap, a delay until the following scan, was provided after each volume for presenting the stimuli and for recording the verbal responses from the dichotic listening task (van den Noort, Specht, Rimol, Ersland, & Hugdahl, 2008).

After the dichotic listening task, participants waited for 90 s in a quiet position until tDCS terminated. Then, the electrode cables were detached from the inner electrode box and the two remaining PRESS sequences were carried out. One participant with dyslexia was removed from the analysis including dichotic listening data because dyslexia might be associated with aberrant hemispheric asymmetry and/or performance in the forced attention conditions (Breznitz & Misra, 2003; Thomson, 1976).

2.2.5 | Adverse side effects

Side effects were measured with the tDCS Adverse Effects Questionnaire (Brunoni et al., 2011) after both sham and real tDCS sessions (Appendix S1).

2.3 | Data analysis

SPSS Statistics (version 25) and Statistica (version 13.3) were used for statistical analysis.

2.3.1 | Dichotic listening and fMRI

Correctly identified syllables were transformed into accuracy rates and subjected to a 2 × 3 × 2 repeated measures ANOVA with the within-participants variables *Stimulation* (real/sham), *Dichotic Listening Condition* (non-forced, forced-right, forced-left) and *Ear* (left/right). Similarly for the fMRI group analysis, individual contrast images were subjected to a 2 × 3 repeated measures ANOVA with *Stimulation* (real/sham) and *Dichotic Listening Condition* (non-forced, forced-right, forced-left). A mean contrast was estimated for illustrating the overall activation pattern across all conditions and for comparisons with earlier studies. This was supplemented with differential and interaction contrasts. For more details regarding preprocessing of

fMRI data in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/), see Appendix S1. For dichotic listening and spectroscopy data, estimated marginal means are provided.

2.3.2 | MR spectroscopy

Water-scaled, tissue-content-adjusted Glx levels from LCModel (Appendix S1) were subjected to a 2 × 2 × 2 repeated measures ANOVA with the within-participants factors *Stimulation* (real/sham), *Time* (before/after tDCS) and *Brain area* (DLPFC/TPC). In four participants, MRS data from one voxel did not meet the data quality requirements. To retain the data from the other voxel with sufficient quality, we additionally calculated two *Time* x *Stimulation* ANOVAs separately for the left DLPFC ($n = 35$) and TPC ($n = 33$). For explorative reasons, we also ran the aforementioned 2 × 2 × 2 ANOVA with choline, creatine, myo-inositol and NAA levels.

2.3.3 | Simulation of electrical field during tDCS

Simulation (done in SimNIBS 2.1.2, Simulation of NIBS [non-invasive brain] stimulation [Version 2.1.2, Software] available from www.simnibs.org) of the tDCS electrical field in each participant was done based on their real tDCS session. To run the model, the electrodes in the simulation were placed over the real electrodes on the participants' head model. The simulated electrodes were 5×7 cm^2, like the real ones, with a 1 mm electrode thickness and 3 mm gel. The electric field strength (in [V/m]) and the focality (in cubic mm) of the stimulation were calculated for the entire cortex and the peak activation field (10 mm sphere). For field strength, 99% of the norm of the electric field and for focality the gray matter volume with an electric field greater or equal to 75% of the peak value are reported. Means and *SD* were calculated.

2.3.4 | Relationship between changes in Glx, dichotic listening accuracy, field strength, and focality

We computed a normality test for all variables and found some with non-normal distribution; hence, Spearman Rank correlations were computed between Glx and myo-inositol levels from before and after real stimulation as well as changes in Glx/myo-inositol levels (as calculated with Glx/myo-inositol$_{\text{pre-tDCS}}$ minus Glx/myo-inositol$_{\text{post-tDCS}}$), separately for DLPFC and TPC, with (a) field strength and focality from the simulation data and (b) the total number of correct responses in the non-forced, forced-right and forced-left condition. All measures were taken from the real tDCS session. As tDCS had no significant effect on fMRI data (see below), no correlations involving fMRI data were computed.

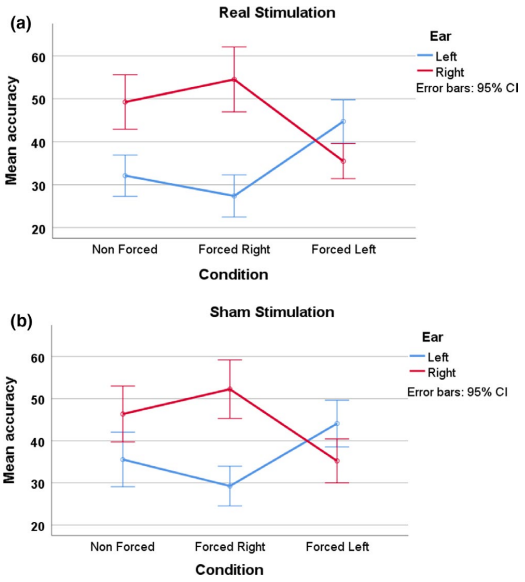

FIGURE 3 Mean accuracy scores (estimated marginal means) for dichotic listening. Panel a) Real tDCS stimulation. Panel b) sham stimulation.

3 | RESULTS

3.1 | Simultaneous Dichotic Listening and fMRI paradigm

3.1.1 | Dichotic listening behavior

The behavioral data revealed a significant main effect of Ear ($F_{(1,30)} = 5.63$, $p = .024$, $\eta_p 2 = .158$), showing that participants reported more syllables correctly from the right ($M = 45.51 \pm 13.86$) than the left ear ($M = 35.51 \pm 10.91$). There was also a significant Condition*Ear interaction ($F_{(1,30)} = 40.28$, $p < .0001$, $\eta_p^2 = .573$) with a substantial right ear advantage in the non-forced and forced-right condition, while a left ear advantage emerged in the forced-left condition (Figure 3). However, neither the main effect of Stimulation nor any interaction involving Stimulation reached significance (all $Fs \leq 1.64$, $ps \geq .203$, $\eta_p^2 s \leq .052$).

3.1.2 | fMRI

For the fMRI data, a mean contrast across all variables in the ANOVA (Figure 4a) showed activity in the auditory

cortex and the left DLPFC. Moreover, we found a main effect of Condition, showing two main significant clusters, one in the left cerebral white matter and precuneus (location in mm: $x = -10$ $y = -60$ $z = 52$, cluster level: #voxel = 1,739, p(FWE) < 0.001, peak: $F_{(2,186)} = 20.73$ p(FWE) < 0.001) and one in the right lingual gyrus and cerebellum exterior (location in mm: $x = 10$ $y = -64$ $z = -8$, cluster level: #voxel = 285, p(FWE) < 0.001, peak: $F_{(2,186)} = 21.71$, p(FWE) < 0.001; Figure 4b). There was also a significant cluster in the forced-right versus forced-left contrast in the right lingual gyrus and cerebellum exterior (location in mm: $x = 10$ $y = -64$ $z = -8$, cluster level: #voxel = 377, p(FWE) <0.001, peak: $T_{(1,186)} = 6.30$, p(FWE) < 0.001; Figure 4c). No significant suprathreshold clusters emerged for the main effect of Stimulation or the interaction between Conditions*Stimulation (all $Ts \leq 2.66$, $p_{\text{FWE-corr}} \geq 0.999$, $p_{\text{uncorr}} \geq 0.004$).

3.1.3 | MR spectroscopy

Glx showed a trend for a Stimulation*Time interaction ($F_{(1,31)} = 3.35$, $p = .077$, $\eta_p^2 = .098$). Glx levels were higher after tDCS than before when participants received real tDCS, while there was a very minor decrease during sham tDCS (Figure 2c). However, exploratory post hoc t-tests (unadjusted) did not find a significant difference between before and after real tDCS ($p = .109$) and sham tDCS ($p = .356$). As there was no significant three-way interaction ($F_{(1,31)} = 0.002$, $p = .961$, $\eta_p^2 < .001$), this Glx change did not differ between left TPC and DLPFC. Except for a main effect of *Brain area* ($F_{(1,31)} = 14.19$, $p = .001$, $\eta_p^2 = .314$), with higher Glx levels in the left DLPFC ($M = 11.45 \pm 1.47$) as compared to the left TPC ($M = 12.84 \pm 1.47$), no other main effect or interaction reached significance (all $F \leq 0.367$, $p \geq .549$, $\eta_p^2 \leq .012$). Likewise, there were no significant main effects or interactions in the 2 × 2 ANOVA for either left DLPFC or TPC (all $F \leq 2.013$, $p \geq .166$, $\eta_p^2 \leq .059$).

None of the other metabolites or parameters (choline, creatine and NAA) showed a significant main effect or interaction involving the factor Stimulation, except for myo-inositol, where a Stimulation*Time interaction emerged ($F_{(1,31)} = 4.59$, $p = .040$, $\eta_p^2 = .129$). Real tDCS led to an increase from $M = 5.34 \pm 0.53$ I.U. to $M = 5.47 \pm 0.57$ I.U., while there was a small decrease in sham tDCS from $M = 5.40 \pm 0.72$ I.U. to $M = 5.29 \pm 0.65$ I.U., uncorrected post hoc tests showed neither were significant. The difference between real and sham tDCS after stimulation was significant ($p = .032$).

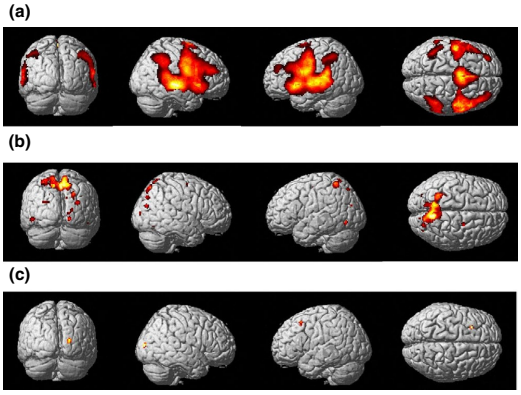

FIGURE 4 fMRI activity during dichotic listening. Panel a) Contrast across all variables in ANOVA. Panel b) Main effect dichotic listening condition. Panel c) Contrast forced-right vs. forced-left condition.

3.2 | Simulation of electrical field during tDCS

The simulated electric field strengths of all participants were strongest in the left central sulcus region and Broca's area, though with considerable inter-individual differences (Appendix S1). For the full cortex, the 99% peak field was $M = 0.65 \pm 0.096$ V/m and 75% focality was $M = 9{,}716 \pm 2045$ mm^2. For the Peak, the 99% peak field was $M = 0.77 \pm 0.144$ V/m and 75% focality was $M = 274 \pm 142$ mm^2.

3.3 | Correlations

Glx levels before/after tDCS as well as Glx changes between before/after did not correlate with either dichotic listening (all rs $\leq .345$, ps $\geq .057$) or simulated field strength and focality (all rs $\leq .234$, ps $\geq .197$). Similarly, myo-inositol levels before/after tDCS as well as myo-inositol changes did not correlate with dichotic listening (all rs $\leq -.271$, ps $\geq .140$). Myo-inositol changes did not correlate with simulated field strength and focality (all rs $\leq -.197$, ps $\geq .280$). There was one significant correlation, uncorrected for multiple testing, between focality of the simulated field and myo-inositol levels in the TPC before tDCS ($r \leq -.422$, $p \geq .016$), which would not withstand Bonferroni correction. All other correlations between myo-inositol levels before/after tDCS with focality and simulated field strength were not significant (all rs $\leq -.177$, ps $\geq .332$).

3.4 | Blinding and adverse side effects

When asked after the second session to indicate when they received real stimulation, 42% of participants responded

incorrectly (blinding data from one participant was missing). A binominal test found no statistically significant difference from 50% chance level ($p = .473$), implying that the blinding worked by and large. Results on adverse side effects are reported in the Appendix S1.

3.5 | Power analysis

A G*Power analysis (Faul, Erdfelder, Buchner, & Lang, 2009) suggests that to obtain a significant Time*Stimulation interaction with $n = 32$, one would need a medium effect size of $f = 0.26$ (with the settings: power = 0.80, $\alpha = .05$, number of groups = 1, number of measurements = 2, corr among rep measures = 0.5, nonsphericity correction = 1).

4 | DISCUSSION

The present study aimed to elucidate the underlying mechanisms of tDCS effects with a multimodal approach in areas beyond the rather well-researched primary motor/sensory cortex (Antal et al., 2012; Antonenko et al., 2019; Kim et al., 2014; Stagg et al., 2009). We expected a reduced right ear advantage/fewer correct responses in dichotic listening and increased Glx levels/functional activity in the TPC as well as reduced Glx levels/functional activity in the DLPFC during tDCS as compared to sham. However, we found no effects of tDCS on behavior and functional activity and only a trend towards a Glx increase after tDCS. There were only very weak correlations between Glx/myo-inositol levels and dichotic listening and simulated electrical field parameters, if any.

The mean contrast across all dichotic listening fMRI conditions replicated previous findings: Behaviorally, a right ear advantage arose that was modulated by instructions to focus attention on either the left or right ear stimulus (Bless et al., 2013; Hugdahl & Hammar, 1997). We further replicated increased functional activity in typical fronto-temporo-parietal language perception and attention areas (Noort et al., 2008; van den Kompus et al., 2012). Crucially, however, neither dichotic listening performance nor fMRI activity was significantly affected by tDCS. The negative behavioral performance results are in line with a previous study that did not find tDCS effects on dichotic listening after anodal and cathodal stimulation over the left auditory cortex (D'Anselmo, Prete, Tommasi, & Brancucci, 2015). tDCS effects on functional activity during dichotic listening have not been investigated before. In the primary motor cortex, tDCS also did not affect fMRI activity but led to reduced activity in the adjacent supplementary motor cortex (Antal et al., 2011). Finally, while our null findings do not support the hypertemporal/hypofrontal model (Hugdahl, 2015), they also do not invalidate it.

The weak increase in Glx after tDCS was independent of the electrode/brain area. This is inconsistent with findings showing increased Glx levels only after anodal stimulation (2 mA) of the right parietal cortex (Clark et al., 2011; Hunter et al., 2015) or decreased Glx levels only after cathodal tDCS (1 mA) of the motor cortex (Stagg et al., 2009). Our finding is in line, however, with other studies that failed to detect tDCS induced changes in Glx in the primary motor and sensorimotor cortex, posterior superior temporal gyrus and cerebellar cortex at both 1 and 2 mA (Antonenko et al., 2017; Dwyer et al., 2018; Jalali, Chowdhury, Wilson, Miall, & Galea, 2018; Kim et al., 2014; Zappasodi et al., 2017). Another study found increased Glx levels in the striatum during tDCS (1 mA) over the left and right DLPFC (Hone-Blanchet, Edden, & Fecteau, 2016). The inconsistent results are likely to arise from differences in stimulation intensity and electrode location, for instance. However, spurious findings with small samples also constitute a problem: some tDCS/spectroscopy studies have sample sizes around $n = 10$, which is plainly underpowered as recently demonstrated (Sanaei Nezhad et al., 2020).

The most parsimonious explanation for the weak dichotic listening behavioral, Glx and fMRI effects is that the electric current was too low to induce meaningful changes. However, there was a significant, electrode-independent increase of myo-inositol levels, in line with a previous study (Rango et al., 2008). Moreover, glutamate changes were reported in the sensorimotor cortex (Antonenko et al., 2019) and on motor learning in tDCS over primary motor cortex (Naros et al., 2016) with 1 mA—thus, in principal, lower electric field strength than in the present study. Finally, since the correlations between electric field parameters and dichotic listening performance as well as the MRS measures were either non-significant (or would become non-significant if adjusted for multiple testing), stronger electric field parameters might not have necessarily produced stronger tDCS effects.

Another possibility is test power. Our study has a reasonable sample size compared to previous studies. We cannot conclude that tDCS with the parameters described here has no effect at all. However, if it exists, the effect is likely to be small (at best medium) according to our power analysis.

A third possibility is that we failed to detect significant tDCS effects because the peak of the electric field was between the two electrodes, and not in the stimulated left DLPFC and TPC itself. While this could explain the lack of clear Glx-results, it is difficult to reconcile with the significant increase of myo-inositol levels in the left DLPFC and TPC, and with the fact that we did not observe any changes in functional activity in the left central sulcus/Broca's area.

Meta-analyses showed that cathodal tDCS in the DLPFC has little effect on cognitive tasks (Dedoncker, Brunoni,

Baeken, & Vanderhasselt, 2016) and that the cathode rarely induces inhibitory effects in cognitive tasks (Jacobson, Koslowsky, & Lavidor, 2012). In the auditory and posterior temporal cortex, performance in dichotic listening (D'Anselmo et al., 2015) as well as in reading and naming tasks (Westwood et al., 2017) was found to be unaffected by tDCS, and anodal stimulation of the posterior superior temporal gyrus did not change Glx levels (Dwyer et al., 2018). On the other hand, anodal tDCS over the temporo-parietal junction had behavioral effects on reality monitoring (Mondino, Poulet, Suaud-Chagny, & Brunelin, 2016) and tDCS over the DLPFC yields promising findings with respect to depression treatment (Mutz, Edgcumbe, Brunoni, & Fu, 2018; Palm, Hasan, Strube, & Padberg, 2016). Taken together, the DLPFC and TPC can evidently be affected by tDCS, but given the considerable body of null findings together with the present findings, it seems that at least the posterior temporal-parietal region might be less responsive to tDCS than, for instance, the primary sensory/motor cortex. This might make tDCS treatments targeting posterior temporal-parietal areas more challenging (e.g., in schizophrenia or tinnitus).

4.1 | Limitations

Since the structural MR scans were taken with the electrodes on, the electrodes were included in the modelling of the electric field parameters as part of the head. While this affects the thickness of skin and skull in the model, it does so for all participants and should not meaningfully affect the results of the simulation (G.B. Saturnino, A. Thielscher, personal communication, April 08, 2019). We placed the MRS voxels as closely under the electrodes as possible to measure tDCS effects. However, moving the voxel deeper into the brain, especially in the TPC, would have given better MRS measurements. We further avoided high CSF involvement by adding saturation bands, but this does not protect against signal loss from participants' movements.

Moreover, whilst the sample size is relatively large for a study of this nature, it is still small for correlational work and, finally, the effect of stimulation intensity needs further elaboration. A recent study (Samani, Agboada, Jamil, Kuo, & Nitsche, 2019) showed that at 2 mA the cathode might not have an inhibitory but excitatory effect—which is in fact in line with our increased Glx levels under the cathode. Thus, cathodal stimulation at 1 mA could have yielded different results.

In conclusion, we found at best weak effects of tDCS over the left DLPFC and TPC on behavior, glutamate, and functional activity. This is unlikely due to insufficient electric current but, together with other findings, could reflect that the stimulated regions, especially the left TPC, are less sensitive to tDCS than primary sensory/motor areas. Although such weak findings are naturally limited in terms of their scientific contribution, we still think they are relevant—especially in the field of brain stimulation, which due to its fast growth and popularity is sometimes subject to findings that raise replication issues: First, the present study further emphasizes that findings from the primary sensory/motor cortex cannot easily be generalized to other brain regions. Second, it demonstrates that multimodal approaches that combine behavioral with multiple neuroscientific assessments are feasible, in principle. Such studies are rare to date, but clearly have the potential to deepen our understanding the underlying mechanisms of tDCS.

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CONFLICT OF INTEREST

The authors Kenneth Hugdahl, Karsten Specht, and Alexander R. Craven have stock in NordicNeuroLab (NNL) AS, which produced MR accessories used during data acquisition. Otherwise there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: MH, KH, IK and LM. Acquisition of data: MH, IK, AC, and LM. Analysis and interpretation, writing of article: MH, AC, KP and LM. Critical review of article and agreement to be accountable for all aspects of the work: MH, KP, KH, IK, AC, and LM.

DATA AVAILABILITY STATEMENT

Anonymized data will be made available to colleagues upon request to the corresponding author.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ejn.14932

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Doctoral Theses at The Faculty of Psychology, University of Bergen

1980	Allen, Hugh M., Dr. philos.	Parent-offspring interactions in willow grouse (Lagopus L. Lagopus).
1981	Myhrer, Trond, Dr. philos.	Behavioral Studies after selective disruption of hippocampal inputs in albino rats.
1982	Svebak, Sven, Dr. philos.	The significance of motivation for task-induced tonic physiological changes.
1983	Myhre, Grete, Dr. philos.	The Biopsychology of behavior in captive Willow ptarmigan.
	Eide, Rolf, Dr. philos.	PSYCHOSOCIAL FACTORS AND INDICES OF HEALTH RISKS. The relationship of psychosocial conditions to subjective complaints, arterial blood pressure, serum cholesterol, serum triglycerides and urinary catecholamines in middle aged populations in Western Norway.
	Værnes, Ragnar J., Dr. philos.	Neuropsychological effects of diving.
1984	Kolstad, Arnulf, Dr. philos.	Til diskusjonen om sammenhengen mellom sosiale forhold og psykiske strukturer. En epidemiologisk undersøkelse blant barn og unge.
	Løberg, Tor, Dr. philos.	Neuropsychological assessment in alcohol dependence.
1985	Hellesnes, Tore, Dr. philos.	Læring og problemløsning. En studie av den perseptuelle analysens betydning for verbal læring.
	Håland, Wenche, Dr. philos.	Psykoterapi: relasjon, utviklingsprosess og effekt.
1986	Hagtvet, Knut A., Dr. philos.	The construct of test anxiety: Conceptual and methodological issues.
	Jellestad, Finn K., Dr. philos.	Effects of neuron specific amygdala lesions on fear-motivated behavior in rats.
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1988	Kaufmann, Astrid, Dr. philos.	Antisosial atferd hos ungdom. En studie av psykologiske determinanter.

	Mykletun, Reidar J., Dr. philos.	Teacher stress: personality, work-load and health.
	Havik, Odd E., Dr. philos.	After the myocardial infarction: A medical and psychological study with special emphasis on perceived illness.
1989	Bråten, Stein, Dr. philos.	Menneskedyaden. En teoretisk tese om sinnets dialogiske natur med informasjons- og utviklingspsykologiske implikasjoner sammenholdt med utvalgte spedbarnsstudier.
	Wold, Bente, Dr. psychol.	Lifestyles and physical activity. A theoretical and empirical analysis of socialization among children and adolescents.
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1991	Alsaker, Françoise D., Dr. philos.	Global negative self-evaluations in early adolescence.
	Kraft, Pål, Dr. philos.	AIDS prevention in Norway. Empirical studies on diffusion of knowledge, public opinion, and sexual behaviour.
	Endresen, Inger M., Dr. philos.	Psychoimmuniological stress markers in working life.
	Faleide, Asbjørn O., Dr. philos.	Asthma and allergy in childhood. Psychosocial and psychotherapeutic problems.
1992	Dalen, Knut, Dr. philos.	Hemispheric asymmetry and the Dual-Task Paradigm: An experimental approach.
	Bø, Inge B., Dr. philos.	Ungdoms sosiale økologi. En undersøkelse av 14-16 åringers sosiale nettverk.
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	Torgersen, Anne M., Dr. philos.	Genetic and environmental influence on temperamental behaviour. A longitudinal study of twins from infancy to adolescence.
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	Midthassel, Unni Vere, Dr. philos.	Teacher involvement in school development activity. A study of teachers in Norwegian compulsory schools
	Kallestad, Jan Helge, Dr. philos.	Teachers, schools and implementation of the Olweus Bullying Prevention Program.
H	Ofte, Sonja Helgesen, Dr. psychol.	Right-left discrimination in adults and children.
	Netland, Marit, Dr. psychol.	Exposure to political violence. The need to estimate our estimations.
	Diseth, Åge, Dr. psychol.	Approaches to learning: Validity and prediction of academic performance.
	Bjuland, Raymond, Dr. philos.	Problem solving in geometry. Reasoning processes of student teachers working in small groups: A dialogical approach.
2003 V	Arefjord, Kjersti, Dr. psychol.	After the myocardial infarction – the wives' view. Short- and long-term adjustment in wives of myocardial infarction patients.
	Ingjaldsson, Jón Þorvaldur, Dr. psychol.	Unconscious Processes and Vagal Activity in Alcohol Dependency.
	Holden, Børge, Dr. philos.	Følger av atferdsanalytiske forklaringer for atferdsanalysens tilnærming til utforming av behandling.
	Holsen, Ingrid, Dr. philos.	Depressed mood from adolescence to 'emerging adulthood'. Course and longitudinal influences of body image and parent-adolescent relationship.
	Hammar, Åsa Karin, Dr. psychol.	Major depression and cognitive dysfunction- An experimental study of the cognitive effort hypothesis.
	Sprugevica, Ieva, Dr. philos.	The impact of enabling skills on early reading acquisition.
	Gabrielsen, Egil, Dr. philos.	LESE FOR LIVET. Lesekompetansen i den norske voksenbefolkningen sett i lys av visjonen om en enhetsskole.
H	Hansen, Anita Lill, Dr. psychol.	The influence of heart rate variability in the regulation of attentional and memory processes.
	Dyregrov, Kari, Dr. philos.	The loss of child by suicide, SIDS, and accidents: Consequences, needs and provisions of help.
2004 V	Torsheim, Torbjørn, Dr. psychol.	Student role strain and subjective health complaints: Individual, contextual, and longitudinal perspectives.

	Haugland, Bente Storm Mowatt Dr. psychol.	Parental alcohol abuse. Family functioning and child adjustment.
	Milde, Anne Marita, Dr. psychol.	Ulcerative colitis and the role of stress. Animal studies of psychobiological factors in relationship to experimentally induced colitis.
	Stornes, Tor, Dr. philos.	Socio-moral behaviour in sport. An investigation of perceptions of sportspersonship in handball related to important factors of socio-moral influence.
	Mæhle, Magne, Dr. philos.	Re-inventing the child in family therapy: An investigation of the relevance and applicability of theory and research in child development for family therapy involving children.
	Kobbeltvedt, Therese, Dr. psychol.	Risk and feelings: A field approach.
2004 H	Thomsen, Tormod, Dr. psychol.	Localization of attention in the brain.
	Løberg, Else-Marie, Dr. psychol.	Functional laterality and attention modulation in schizophrenia: Effects of clinical variables.
	Kyrkjebø, Jane Mikkelsen, Dr. philos.	Learning to improve: Integrating continuous quality improvement learning into nursing education.
	Laumann, Karin, Dr. psychol.	Restorative and stress-reducing effects of natural environments: Experiencal, behavioural and cardiovascular indices.
	Holgersen, Helge, PhD	Mellom oss - Essay i relasjonell psykoanalyse.
2005 V	Hetland, Hilde, Dr. psychol.	Leading to the extraordinary? Antecedents and outcomes of transformational leadership.
	Iversen, Anette Christine, Dr. philos.	Social differences in health behaviour: the motivational role of perceived control and coping.
2005 H	Mathisen, Gro Ellen, PhD	Climates for creativity and innovation: Definitions, measurement, predictors and consequences.
	Sævi, Tone, Dr. philos.	Seeing disability pedagogically – The lived experience of disability in the pedagogical encounter.
	Wiium, Nora, PhD	Intrapersonal factors, family and school norms: combined and interactive influence on adolescent smoking behaviour.
	Kanagaratnam, Pushpa, PhD	Subjective and objective correlates of Posttraumatic Stress in immigrants/refugees exposed to political violence.
	Larsen, Torill M. B. , PhD	Evaluating principals` and teachers` implementation of Second Step. A case study of four Norwegian primary schools.
	Bancila, Delia, PhD	Psychosocial stress and distress among Romanian adolescents and adults.
2006 V	Hillestad, Torgeir Martin, Dr. philos.	Normalitet og avvik. Forutsetninger for et objektivt psykopatologisk avviksbegrep. En psykologisk, sosial, erkjennelsesteoretisk og teorihistorisk framstilling.

	Nordanger, Dag Øystein, Dr. psychol.	Psychosocial discourses and responses to political violence in post-war Tigray, Ethiopia.
	Rimol, Lars Morten, PhD	Behavioral and fMRI studies of auditory laterality and speech sound processing.
	Krumsvik, Rune Johan, Dr. philos.	ICT in the school. ICT-initiated school development in lower secondary school.
	Norman, Elisabeth, Dr. psychol.	Gut feelings and unconscious thought: An exploration of fringe consiousness in implicit cognition.
	Israel, K Pravin, Dr. psychol.	Parent involvement in the mental health care of children and adolescents. Emperical studies from clinical care setting.
	Glasø, Lars, PhD	Affects and emotional regulation in leader-subordinate relationships.
	Knutsen, Ketil, Dr. philos.	HISTORIER UNGDOM LEVER – En studie av hvordan ungdommer bruker historie for å gjøre livet meningsfullt.
	Matthiesen, Stig Berge, PhD	Bullying at work. Antecedents and outcomes.
2006 H	Gramstad, Arne, PhD	Neuropsychological assessment of cognitive and emotional functioning in patients with epilepsy.
	Bendixen, Mons, PhD	Antisocial behaviour in early adolescence: Methodological and substantive issues.
	Mrumbi, Khalifa Maulid, PhD	Parental illness and loss to HIV/AIDS as experienced by AIDS orphans aged between 12-17 years from Temeke District, Dar es Salaam, Tanzania: A study of the children's psychosocial health and coping responses.
	Hetland, Jørn, Dr. psychol.	The nature of subjective health complaints in adolescence: Dimensionality, stability, and psychosocial predictors
	Kakoko, Deodatus Conatus Vitalis, PhD	Voluntary HIV counselling and testing service uptake among primary school teachers in Mwanza, Tanzania: assessment of socio-demographic, psychosocial and socio-cognitive aspects
	Mykletun, Arnstein, Dr. psychol.	Mortality and work-related disability as long-term consequences of anxiety and depression: Historical cohort designs based on the HUNT-2 study
	Sivertsen, Børge, PhD	Insomnia in older adults. Consequences, assessment and treatment.
2007 V	Singhammer, John, Dr. philos.	Social conditions from before birth to early adulthood – the influence on health and health behaviour
	Janvin, Carmen Ani Cristea, PhD	Cognitive impairment in patients with Parkinson's disease: profiles and implications for prognosis
	Braarud, Hanne Cecilie, Dr.psychol.	Infant regulation of distress: A longitudinal study of transactions between mothers and infants
	Tveito, Torill Helene, PhD	Sick Leave and Subjective Health Complaints

	Magnussen, Liv Heide, PhD	Returning disability pensioners with back pain to work
	Thuen, Elin Marie, Dr.philos.	Learning environment, students' coping styles and emotional and behavioural problems. A study of Norwegian secondary school students.
	Solberg, Ole Asbjørn, PhD	Peacekeeping warriors – A longitudinal study of Norwegian peacekeepers in Kosovo
2007 H	Søreide, Gunn Elisabeth, Dr.philos.	Narrative construction of teacher identity
	Svensen, Erling, PhD	WORK & HEALTH. Cognitive Activation Theory of Stress applied in an organisational setting.
	Øverland, Simon Nygaard, PhD	Mental health and impairment in disability benefits. Studies applying linkages between health surveys and administrative registries.
	Eichele, Tom, PhD	Electrophysiological and Hemodynamic Correlates of Expectancy in Target Processing
	Børhaug, Kjetil, Dr.philos.	Oppseding til demokrati. Ein studie av politisk oppseding i norsk skule.
	Eikeland, Thorleif, Dr.philos.	Om å vokse opp på barnehjem og på sykehus. En undersøkelse av barnehjemsbarns opplevelser på barnehjem sammenholdt med sanatoriebarns beskrivelse av langvarige sykehusopphold – og et forsøk på forklaring.
	Wadel, Carl Cato, Dr.philos.	Medarbeidersamhandling og medarbeiderledelse i en lagbasert organisasjon
	Vinje, Hege Forbech, PhD	Thriving despite adversity: Job engagement and self-care among community nurses
	Noort, Maurits van den, PhD	Working memory capacity and foreign language acquisition
2008 V	Breivik, Kyrre, Dr.psychol.	The Adjustment of Children and Adolescents in Different Post-Divorce Family Structures. A Norwegian Study of Risks and Mechanisms.
	Johnsen, Grethe E., PhD	Memory impairment in patients with posttraumatic stress disorder
	Sætrevik, Bjørn, PhD	Cognitive Control in Auditory Processing
	Carvalhosa, Susana Fonseca, PhD	Prevention of bullying in schools: an ecological model
2008 H	Brønnick, Kolbjørn Selvåg	Attentional dysfunction in dementia associated with Parkinson's disease.
	Posserud, Maj-Britt Rocio	Epidemiology of autism spectrum disorders
	Haug, Ellen	Multilevel correlates of physical activity in the school setting
	Skjerve, Arvid	Assessing mild dementia – a study of brief cognitive tests.

	Kjønniksen, Lise	The association between adolescent experiences in physical activity and leisure time physical activity in adulthood: a ten year longitudinal study
	Gundersen, Hilde	The effects of alcohol and expectancy on brain function
	Omvik, Siri	Insomnia – a night and day problem
2009 V	Molde, Helge	Pathological gambling: prevalence, mechanisms and treatment outcome.
	Foss, Else	Den omsorgsfulle væremåte. En studie av voksnes væremåte i forhold til barn i barnehagen.
	Westrheim, Kariane	Education in a Political Context: A study of Konwledge Processes and Learning Sites in the PKK.
	Wehling, Eike	Cognitive and olfactory changes in aging
	Wangberg, Silje C.	Internet based interventions to support health behaviours: The role of self-efficacy.
	Nielsen, Morten B.	Methodological issues in research on workplace bullying. Operationalisations, measurements and samples.
	Sandu, Anca Larisa	MRI measures of brain volume and cortical complexity in clinical groups and during development.
	Guribye, Eugene	Refugees and mental health interventions
	Sørensen, Lin	Emotional problems in inattentive children – effects on cognitive control functions.
	Tjomsland, Hege E.	Health promotion with teachers. Evaluation of the Norwegian Network of Health Promoting Schools: Quantitative and qualitative analyses of predisposing, reinforcing and enabling conditions related to teacher participation and program sustainability.
	Helleve, Ingrid	Productive interactions in ICT supported communities of learners
2009 H	Skorpen, Aina Øye, Christine	Dagliglivet i en psykiatrisk institusjon: En analyse av miljøterapeutiske praksiser
	Andreassen, Cecilie Schou	WORKAHOLISM – Antecedents and Outcomes
	Stang, Ingun	Being in the same boat: An empowerment intervention in breast cancer self-help groups
	Sequeira, Sarah Dorothee Dos Santos	The effects of background noise on asymmetrical speech perception
	Kleiven, Jo, dr.philos.	The Lillehammer scales: Measuring common motives for vacation and leisure behavior
	Jónsdóttir, Guðrún	Dubito ergo sum? Ni jenter møter naturfaglig kunnskap.
	Hove, Oddbjørn	Mental health disorders in adults with intellectual disabilities - Methods of assessment and prevalence of mental health disorders and problem behaviour
	Wageningen, Heidi Karin van	The role of glutamate on brain function

	Bjørkvik, Jofrid	God nok? Selvaktelse og interpersonlig fungering hos pasienter innen psykisk helsevern: Forholdet til diagnoser, symptomer og behandlingsutbytte
	Andersson, Martin	A study of attention control in children and elderly using a forced-attention dichotic listening paradigm
	Almås, Aslaug Grov	Teachers in the Digital Network Society: Visions and Realities. A study of teachers' experiences with the use of ICT in teaching and learning.
	Ulvik, Marit	Lærerutdanning som danning? Tre stemmer i diskusjonen
2010 V	Skår, Randi	Læringsprosesser i sykepleieres profesjonsutøvelse. En studie av sykepleieres læringserfaringer.
	Roald, Knut	Kvalitetsvurdering som organisasjonslæring mellom skole og skoleeigar
	Lunde, Linn-Heidi	Chronic pain in older adults. Consequences, assessment and treatment.
	Danielsen, Anne Grete	Perceived psychosocial support, students' self-reported academic initiative and perceived life satisfaction
	Hysing, Mari	Mental health in children with chronic illness
	Olsen, Olav Kjellevold	Are good leaders moral leaders? The relationship between effective military operational leadership and morals
	Riese, Hanne	Friendship and learning. Entrepreneurship education through mini-enterprises.
	Holthe, Asle	Evaluating the implementation of the Norwegian guidelines for healthy school meals: A case study involving three secondary schools
H	Hauge, Lars Johan	Environmental antecedents of workplace bullying: A multi-design approach
	Bjørkelo, Brita	Whistleblowing at work: Antecedents and consequences
	Reme, Silje Endresen	Common Complaints – Common Cure? Psychiatric comorbidity and predictors of treatment outcome in low back pain and irritable bowel syndrome
	Helland, Wenche Andersen	Communication difficulties in children identified with psychiatric problems
	Beneventi, Harald	Neuronal correlates of working memory in dyslexia
	Thygesen, Elin	Subjective health and coping in care-dependent old persons living at home
	Aanes, Mette Marthinussen	Poor social relationships as a threat to belongingness needs. Interpersonal stress and subjective health complaints: Mediating and moderating factors.
	Anker, Morten Gustav	Client directed outcome informed couple therapy

	Bull, Torill	Combining employment and child care: The subjective well-being of single women in Scandinavia and in Southern Europe
	Viig, Nina Grieg	Tilrettelegging for læreres deltakelse i helsefremmende arbeid. En kvalitativ og kvantitativ analyse av sammenhengen mellom organisatoriske forhold og læreres deltakelse i utvikling og implementering av Europeisk Nettverk av Helsefremmende Skoler i Norge
	Wolff, Katharina	To know or not to know? Attitudes towards receiving genetic information among patients and the general public.
	Ogden, Terje, dr.philos.	Familiebasert behandling av alvorlige atferdsproblemer blant barn og ungdom. Evaluering og implementering av evidensbaserte behandlingsprogrammer i Norge.
	Solberg, Mona Elin	Self-reported bullying and victimisation at school: Prevalence, overlap and psychosocial adjustment.
2011 V	Bye, Hege Høivik	Self-presentation in job interviews. Individual and cultural differences in applicant self-presentation during job interviews and hiring managers' evaluation
	Notelaers, Guy	Workplace bullying. A risk control perspective.
	Moltu, Christian	Being a therapist in difficult therapeutic impasses. A hermeneutic phenomenological analysis of skilled psychotherapists' experiences, needs, and strategies in difficult therapies ending well.
	Myrseth, Helga	Pathological Gambling - Treatment and Personality Factors
	Schanche, Elisabeth	From self-criticism to self-compassion. An empirical investigation of hypothesized change prosesses in the Affect Phobia Treatment Model of short-term dynamic psychotherapy for patients with Cluster C personality disorders.
	Våpenstad, Eystein Victor, dr.philos.	Det tempererte nærvær. En teoretisk undersøkelse av psykoterapautens subjektivitet i psykoanalyse og psykoanalytisk psykoterapi.
	Haukebø, Kristin	Cognitive, behavioral and neural correlates of dental and intra-oral injection phobia. Results from one treatment and one fMRI study of randomized, controlled design.
	Harris, Anette	Adaptation and health in extreme and isolated environments. From 78°N to 75°S.
	Bjørknes, Ragnhild	Parent Management Training-Oregon Model: intervention effects on maternal practice and child behavior in ethnic minority families
	Mamen, Asgeir	Aspects of using physical training in patients with substance dependence and additional mental distress
	Espevik, Roar	Expert teams: Do shared mental models of team members make a difference
	Haara, Frode Olav	Unveiling teachers' reasons for choosing practical activities in mathematics teaching

2011 H	Hauge, Hans Abraham	How can employee empowerment be made conducive to both employee health and organisation performance? An empirical investigation of a tailor-made approach to organisation learning in a municipal public service organisation.
	Melkevik, Ole Rogstad	Screen-based sedentary behaviours: pastimes for the poor, inactive and overweight? A cross-national survey of children and adolescents in 39 countries.
	Vøllestad, Jon	Mindfulness-based treatment for anxiety disorders. A quantitative review of the evidence, results from a randomized controlled trial, and a qualitative exploration of patient experiences.
	Tolo, Astrid	Hvordan blir lærerkompetanse konstruert? En kvalitativ studie av PPU-studenters kunnskapsutvikling.
	Saus, Evelyn-Rose	Training effectiveness: Situation awareness training in simulators
	Nordgreen, Tine	Internet-based self-help for social anxiety disorder and panic disorder. Factors associated with effect and use of self-help.
	Munkvold, Linda Helen	Oppositional Defiant Disorder: Informant discrepancies, gender differences, co-occuring mental health problems and neurocognitive function.
	Christiansen, Øivin	Når barn plasseres utenfor hjemmet: beslutninger, forløp og relasjoner. Under barnevernets (ved)tak.
	Brunborg, Geir Scott	Conditionability and Reinforcement Sensitivity in Gambling Behaviour
	Hystad, Sigurd William	Measuring Psychological Resiliency: Validation of an Adapted Norwegian Hardiness Scale
2012 V	Roness, Dag	Hvorfor bli lærer? Motivasjon for utdanning og utøving.
	Fjermestad, Krister Westlye	The therapeutic alliance in cognitive behavioural therapy for youth anxiety disorders
	Jenssen, Eirik Sørnes	Tilpasset opplæring i norsk skole: politikeres, skoleledereres og læreres handlingsvalg
	Saksvik-Lehouillier, Ingvild	Shift work tolerance and adaptation to shift work among offshore workers and nurses
	Johansen, Venke Frederike	Når det intime blir offentlig. Om kvinners åpenhet om brystkreft og om markedsføring av brystkreftsaken.
	Herheim, Rune	Pupils collaborating in pairs at a computer in mathematics learning: investigating verbal communication patterns and qualities
	Vie, Tina Løkke	Cognitive appraisal, emotions and subjective health complaints among victims of workplace bullying: A stress-theoretical approach
	Jones, Lise Øen	Effects of reading skills, spelling skills and accompanying efficacy beliefs on participation in education. A study in Norwegian prisons.

2012 H	Danielsen, Yngvild Sørebø	Childhood obesity – characteristics and treatment. Psychological perspectives.
	Horverak, Jøri Gytre	Sense or sensibility in hiring processes. Interviewee and interviewer characteristics as antecedents of immigrant applicants' employment probabilities. An experimental approach.
	Jøsendal, Ola	Development and evaluation of BE smokeFREE, a school-based smoking prevention program
	Osnes, Berge	Temporal and Posterior Frontal Involvement in Auditory Speech Perception
	Drageset, Sigrunn	Psychological distress, coping and social support in the diagnostic and preoperative phase of breast cancer
	Aasland, Merethe Schanke	Destructive leadership: Conceptualization, measurement, prevalence and outcomes
	Bakibinga, Pauline	The experience of job engagement and self-care among Ugandan nurses and midwives
	Skogen, Jens Christoffer	Foetal and early origins of old age health. Linkage between birth records and the old age cohort of the Hordaland Health Study (HUSK)
	Leversen, Ingrid	Adolescents' leisure activity participation and their life satisfaction: The role of demographic characteristics and psychological processes
	Hanss, Daniel	Explaining sustainable consumption: Findings from cross-sectional and intervention approaches
	Rød, Per Arne	Barn i klem mellom foreldrekonflikter og samfunnsmessig beskyttelse
2013 V	Mentzoni, Rune Aune	Structural Characteristics in Gambling
	Knudsen, Ann Kristin	Long-term sickness absence and disability pension award as consequences of common mental disorders. Epidemiological studies using a population-based health survey and official ill health benefit registries.
	Strand, Mari	Emotional information processing in recurrent MDD
	Veseth, Marius	Recovery in bipolar disorder. A reflexive-collaborative exploration of the lived experiences of healing and growth when battling a severe mental illness
	Mæland, Silje	Sick leave for patients with severe subjective health complaints. Challenges in general practice.
	Mjaaland, Thera	At the frontiers of change? Women and girls' pursuit of education in north-western Tigray, Ethiopia
	Odéen, Magnus	Coping at work. The role of knowledge and coping expectancies in health and sick leave.
	Hynninen, Kia Minna Johanna	Anxiety, depression and sleep disturbance in chronic obstructive pulmonary disease (COPD). Associations, prevalence and effect of psychological treatment.

	Flo, Elisabeth	Sleep and health in shift working nurses
	Aasen, Elin Margrethe	From paternalism to patient participation? The older patients undergoing hemodialysis, their next of kin and the nurses: a discursive perspective on perception of patient participation in dialysis units
	Ekornås, Belinda	Emotional and Behavioural Problems in Children: Self-perception, peer relationships, and motor abilities
	Corbin, J. Hope	North-South Partnerships for Health: Key Factors for Partnership Success from the Perspective of the KIWAKKUKI
	Birkeland, Marianne Skogbrott	Development of global self-esteem: The transition from adolescence to adulthood
2013 H	Gianella-Malca, Camila	Challenges in Implementing the Colombian Constitutional Court's Health-Care System Ruling of 2008
	Hovland, Anders	Panic disorder – Treatment outcomes and psychophysiological concomitants
	Mortensen, Øystein	The transition to parenthood – Couple relationships put to the test
	Årdal, Guro	Major Depressive Disorder – a Ten Year Follow-up Study. Inhibition, Information Processing and Health Related Quality of Life
	Johansen, Rino Bandlitz	The impact of military identity on performance in the Norwegian armed forces
	Bøe, Tormod	Socioeconomic Status and Mental Health in Children and Adolescents
2014 V	Nordmo, Ivar	Gjennom nåløyet – studenters læringserfaringer i psykologutdanningen
	Dovran, Anders	Childhood Trauma and Mental Health Problems in Adult Life
	Hegelstad, Wenche ten Velden	Early Detection and Intervention in Psychosis: A Long-Term Perspective
	Urheim, Ragnar	Forståelse av pasientaggresjon og forklaringer på nedgang i voldsrate ved Regional sikkerhetsavdeling, Sandviken sykehus
	Kinn, Liv Grethe	Round-Trips to Work. Qualitative studies of how persons with severe mental illness experience work integration.
	Rød, Anne Marie Kinn	Consequences of social defeat stress for behaviour and sleep. Short-term and long-term assessments in rats.
	Nygård, Merethe	Schizophrenia – Cognitive Function, Brain Abnormalities, and Cannabis Use
	Tjora, Tore	Smoking from adolescence through adulthood: the role of family, friends, depression and socioeconomic status. Predictors of smoking from age 13 to 30 in the "The Norwegian Longitudinal Health Behaviour Study" (NLHB)
	Vangsnes, Vigdis	The Dramaturgy and Didactics of Computer Gaming. A Study of a Medium in the Educational Context of Kindergartens.

	Nordahl, Kristin Berg	Early Father-Child Interaction in a Father-Friendly Context: Gender Differences, Child Outcomes, and Protective Factors related to Fathers' Parenting Behaviors with One-year-olds
2014 H	Sandvik, Asle Makoto	Psychopathy – the heterogenety of the construct
	Skotheim, Siv	Maternal emotional distress and early mother-infant interaction: Psychological, social and nutritional contributions
	Halleland, Helene Barone	Executive Functioning in adult Attention Deficit Hyperactivity Disorder (ADHD). From basic mechanisms to functional outcome.
	Halvorsen, Kirsti Vindal	Partnerskap i lærerutdanning, sett fra et økologisk perspektiv
	Solbue, Vibeke	Dialogen som visker ut kategorier. En studie av hvilke erfaringer innvandrerungdommer og norskfødte med innvandrerforeldre har med videregående skole. Hva forteller ungdommenes erfaringer om videregående skoles håndtering av etniske ulikheter?
	Kvalevaag, Anne Lise	Fathers' mental health and child development. The predictive value of fathers' psychological distress during pregnancy for the social, emotional and behavioural development of their children
	Sandal, Ann Karin	Ungdom og utdanningsval. Om elevar sine opplevingar av val og overgangsprosessar.
	Haug, Thomas	Predictors and moderators of treatment outcome from high- and low-intensity cognitive behavioral therapy for anxiety disorders. Association between patient and process factors, and the outcome from guided self-help, stepped care, and face-to-face cognitive behavioral therapy.
	Sjølie, Hege	Experiences of Members of a Crisis Resolution Home Treatment Team. Personal history, professional role and emotional support in a CRHT team.
	Falkenberg, Liv Eggset	Neuronal underpinnings of healthy and dysfunctional cognitive control
	Mrdalj, Jelena	The early life condition. Importance for sleep, circadian rhythmicity, behaviour and response to later life challenges
	Hesjedal, Elisabeth	Tverrprofesjonelt samarbeid mellom skule og barnevern: Kva kan støtte utsette barn og unge?
2015 V	Hauken, May Aasebø	«*The cancer treatment was only half the work!»* A Mixed-Method Study of Rehabilitation among Young Adult Cancer Survivors
	Ryland, Hilde Katrin	Social functioning and mental health in children: the influence of chronic illness and intellectual function
	Rønsen, Anne Kristin	Vurdering som profesjonskompetanse. Refleksjonsbasert utvikling av læreres kompetanse i formativ vurdering

	Hoff, Helge Andreas	Thinking about Symptoms of Psychopathy in Norway: Content Validation of the Comprehensive Assessment of Psychopathic Personality (CAPP) Model in a Norwegian Setting
	Schmid, Marit Therese	Executive Functioning in recurrent- and first episode Major Depressive Disorder. Longitudinal studies
	Sand, Liv	Body Image Distortion and Eating Disturbances in Children and Adolescents
	Matanda, Dennis Juma	Child physical growth and care practices in Kenya: Evidence from Demographic and Health Surveys
	Amugsi, Dickson Abanimi	Child care practices, resources for care, and nutritional outcomes in Ghana: Findings from Demographic and Health Surveys
	Jakobsen, Hilde	The good beating: Social norms supporting men's partner violence in Tanzania
	Sagoe, Dominic	Nonmedical anabolic-androgenic steroid use: Prevalence, attitudes, and social perception
	Eide, Helene Marie Kjærgård	Narrating the relationship between leadership and learning outcomes. A study of public narratives in the Norwegian educational sector.
2015 H	Wubs, Annegreet Gera	Intimate partner violence among adolescents in South Africa and Tanzania
	Hjelmervik, Helene Susanne	Sex and sex-hormonal effects on brain organization of fronto-parietal networks
	Dahl, Berit Misund	The meaning of professional identity in public health nursing
	Røykenes, Kari	Testangst hos sykepleierstudenter: «Alternativ behandling»
	Bless, Josef Johann	The smartphone as a research tool in psychology. Assessment of language lateralization and training of auditory attention.
	Løvvik, Camilla Margrethe Sigvaldsen	Common mental disorders and work participation – the role of return-to-work expectations
	Lehmann, Stine	Mental Disorders in Foster Children: A Study of Prevalence, Comorbidity, and Risk Factors
	Knapstad, Marit	Psychological factors in long-term sickness absence: the role of shame and social support. Epidemiological studies based on the Health Assets Project.
2016 V	Kvestad, Ingrid	Biological risks and neurodevelopment in young North Indian children
	Sælør, Knut Tore	Hinderløyper, halmstrå og hengende snører. En kvalitativ studie av håp innenfor psykisk helse- og rusfeltet.
	Mellingen, Sonja	Alkoholbruk, partilfredshet og samlivsstatus. Før, inn i, og etter svangerskapet – korrelater eller konsekvenser?
	Thun, Eirunn	Shift work: negative consequences and protective factors

	Hilt, Line Torbjørnsen	The borderlands of educational inclusion. Analyses of inclusion and exclusion processes for minority language students
	Havnen, Audun	Treatment of obsessive-compulsive disorder and the importance of assessing clinical effectiveness
	Slåtten, Hilde	Gay-related name-calling among young adolescents. Exploring the importance of the context.
	Ree, Eline	Staying at work. The role of expectancies and beliefs in health and workplace interventions.
	Morken, Frøydis	Reading and writing processing in dyslexia
2016 H	Løvoll, Helga Synnevåg	Inside the outdoor experience. On the distinction between pleasant and interesting feelings and their implication in the motivational process.
	Hjeltnes, Aslak	Facing social fears: An investigation of mindfulness-based stress reduction for young adults with social anxiety disorder
	Øyeflaten, Irene Larsen	Long-term sick leave and work rehabilitation. Prognostic factors for return to work.
	Henriksen, Roger Ekeberg	Social relationships, stress and infection risk in mother and child
	Johnsen, Iren	«Only a friend» - The bereavement process of young adults who have lost a friend to a traumatic death. A mixed methods study.
	Helle, Siri	Cannabis use in non-affective psychoses: Relationship to age at onset, cognitive functioning and social cognition
	Glambek, Mats	Workplace bullying and expulsion in working life. A representative study addressing prospective associations and explanatory conditions.
	Oanes, Camilla Jensen	Tilbakemelding i terapi. På hvilke måter opplever terapeuter at tilbakemeldingsprosedyrer kan virke inn på terapeutiske praksiser?
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