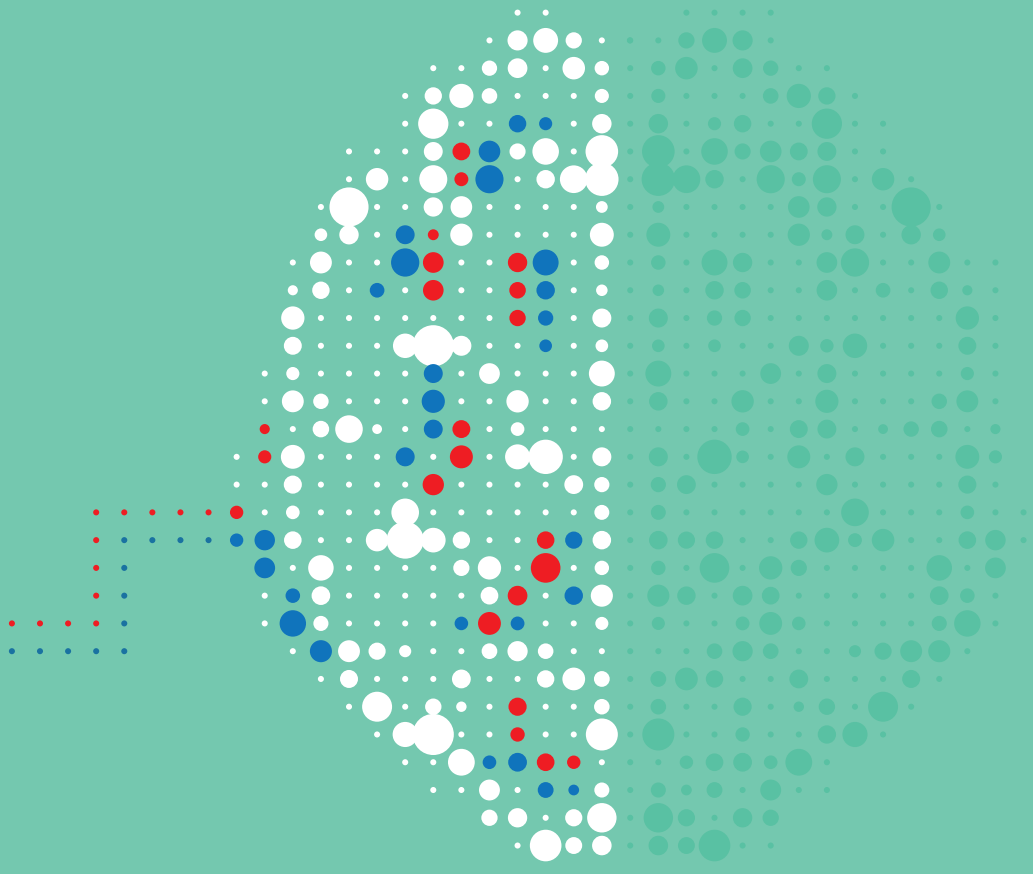

Neuroplasticity in post-stroke aphasia

The effectiveness of Transcranial Direct Current Stimulation

Kerstin Spielmann

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The effectiveness of Transcranial Direct Current Stimulation

Neuroplasticiteit bij afasie na een CVA

Het effect van transcraniële direct current stimulatie

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CONTENTS

CHAPTER 1

General introduction

Aphasia occurs in about 30-40% of the patients immediately after stroke.[1-3] As a consequence, different communication modalities are affected, such as speaking, understanding, reading and writing, with a negative impact on social, vocational and recreational activities. One study found that among 60 diseases and 15 conditions, aphasia showed the largest negative relationship with health-related quality of life, followed by cancer and Alzheimer's disease.[4]

People with aphasia receive Speech and Language Therapy (SLT). The aim of SLT is to improve communication, and in turn to improve quality of life and participation. Although a recent Cochrane review has shown that SLT can be effective to improve functional communication, reading, writing and expressive language,[5] the optimal timing of SLT after stroke still has to be established.[6] In the first months after stroke the brain is in a stage of spontaneous recovery, with a reorganization of function and structure. It is assumed that early SLT interacts with spontaneous recovery.[7, 8] However, studies investigating the effect of early SLT show contradictory results and therefore it remains a challenge to optimize the effectiveness of early SLT.[6, 9]

At present, our understanding of the neurobiology of recovery after stroke and of the individual variability in aphasia outcome, is still limited and even more so are our means to boost neurological recovery beyond the level of spontaneous recovery. One of the main challenges in aphasia rehabilitation therefore is to improve our understanding of the neural basis of spontaneous and treatment-induced recovery after stroke.[10, 11]

NEUROPLASTICITY: THE BRAIN'S POTENTIAL TO COPE WITH DAMAGE

Aphasia is typically caused by damage to a complex language network involving areas in the left hemisphere (LH), which generally is the dominant hemisphere in language processing for most healthy right-handed and left-handed individuals.[11, 12] With a stroke, there is a disruption of blood supply, leading to changes in ionic balance and causing toxic effects and cell death.[10, 13] As a consequence, edema develops, in which brain tissue gets inflamed and swollen. The so-called penumbra is the area around the core lesion area, which is hypo-perfused; permanent damage of this area however can still be prevented by reperfusion.[14, 15] Not only the core lesion area and the surrounding penumbra show physiological disturbances and hypo-metabolism, also areas that are distant but connected to the lesion; this phenomenon is called diaschisis. Different brain mechanisms occur to promote repair and rewiring after stroke.[16] Recovery from aphasia is mediated by these neuroplastic processes. In general, there is stroke-induced neuroplasticity, typi-

cally referred to as spontaneous recovery, and experience-dependent neuroplasticity, which is induced by training or treatment.

Spontaneous recovery

Animal studies have shown that stroke induces a cascade of cellular and molecular events.[17] In the *acute phase (first days)*, there is an increase in dendritic spines, axonal sprouting, angiogenesis (i.e. microvascular growth) and even neurogenesis.[13, 17, 18] Growth factors, such as the Brain-Derived Neurotrophic Factor (BDNF), are increased to promote repair. These processes contribute to saving the penumbra and reducing edema. In the *sub-acute phase (days to weeks)*, resolution of diaschisis takes place.[13] The brain becomes excitable; this increased excitability is present in the perilesional areas surrounding the core lesion area and penumbra,[19, 20] and it promotes *Long Term Potentiation (LTP)*, which refers to the process of long-term enhancement of signal transmission between neurons. LTP enhances synaptic efficiency and is related to learning. LTP is mediated by N-methyl-D-aspartate (NMDA) receptor activity and BDNF. In the *chronic phase*, anatomic remodeling takes place, such as dendritic outgrowth and synaptogenesis,[20] leading to further reorganization that may continue for many years after stroke.

Recovery of aphasia is a dynamic process. Based on a neuroimaging study of recovery in stroke patients with aphasia, Saur et al.[20, 21] described three stages, which are related to the cellular and molecular events that occur successively. In the first stage, the first 4 days post stroke, there is reduced activation in the LH and right hemisphere (RH), related to the presence of diaschisis. At 14 days, a resolution of diaschisis is observed, shown by strong activation in the preserved areas in the LH and RH (bilateral activation), which can be related to the increase in excitability. In the final stage, in 4-12 months, a 're-shift' to the LH is observed, which can be related to anatomic remodeling that underlies reorganization.

An important concept in explaining the recovery process in the language network, is *interhemispheric balance*. In healthy speakers, language processing activates a bilateral network, which is left lateralized in most people. A lesion in the LH causes a reduced inhibitory effect of the LH over the RH, thus disturbing the interhemispheric balance and leading to increased RH activity. Two main concepts are suggested in post-stroke language recovery, *restoration* and *reorganization*. Regaining activity in the damaged areas in the LH would be related with good recovery.[22, 23] This is also referred to as *restoration*, meaning that areas are involved that were also involved before the injury.[24] Second, lost language functions may be taken over either by representational areas around the lesion, i.e. perilesional areas in the LH, or by areas in the RH, i.e. contralateral areas; the latter has been described as 'laterality shift'.[21, 25] Thus, in these intra- and interhemispheric

reorganization processes, areas are recruited that were previously not engaged during language processing.[24] There is an ongoing discussion regarding the involvement of the RH; some studies support the idea that the RH has the potential to process language and that its activation is adaptive,[26-28] while others claim that its activation reflects decreased inhibitory effects from the LH and that it is maladaptive.[29-31] In the literature there is more support for a crucial role of the LH, with many studies supporting the idea that activation of LH perilesional areas is related to good recovery.[17, 32] However, other studies have found support for beneficial RH involvement in post-stroke language recovery, and individual differences have been described, such that the effectiveness of RH recruitment may depend on lesion location and size.[33]

Treatment-induced recovery

Treatment-induced recovery refers to the experience-driven changes on a behavioral and neural level. In general, experience-driven changes underlie learning in the healthy brain, but also re-learning in the case of people with brain damage.[34, 35] Animal studies have shown that training promotes spontaneous recovery processes, in terms of dendritic growth and enhanced synaptic responses.[24] It therefore also promotes LTP, which would in turn be mediated by the activity-dependent release of BDNF.[36] The secretion of BDNF differs across different genotypes, and therefore leads to individual variability in the rate of learning and possibly also in re-learning in the case of stroke. Specifically, stroke outcomes have been related to BDNF secretion, such that people with a specific BDNF genotype may have reduced secretion leading to a less favorable outcome after stroke.[37, 38] However, results are mixed[39, 40] and so far, its influence on aphasia recovery has not been investigated.

The aim of SLT is to restore linguistic functioning and in turn to improve communication in patients with aphasia. In general, treatment in the sub-acute phase starts with cognitive-linguistic treatment (CLT). CLT is used to avoid nonuse and focuses on the impairment level; the aim is to improve the linguistic deficits (semantics, phonology, syntax) that underlie the communication problems.[24] However, the efficacy and optimal timing of CLT is still a matter of debate.[6, 9, 41] Later on in the rehabilitation process, treatment focuses on compensation, providing the patient new ways to use language and compensatory strategies.[35]

Neuroimaging can be used to understand the treatment-induced effects on aphasia recovery. Several studies have shown that treatment-induced recovery, thus language improvement after SLT, is related with increased activity in specific brain areas in the LH.[42-44] These observations support the idea that SLT promotes LH recruitment which in turn is related to successful, adaptive neuroplasticity processes. In the last decades neu-

roimaging studies are used to segregate brain areas whose activation is associated with either adaptive or maladaptive neuroplasticity. Adaptive plasticity can for example be contrasted with maladaptive plasticity by comparing the activation during correct naming with activation related to naming errors. Therefore, these segregation techniques can be used as a guidance for identifying areas involved in adaptive or maladaptive processes. Non-invasive brain stimulation, as described in the following section, can be used to either stimulate cortical areas involved in adaptive processes and/or to inhibit areas involved in maladaptive processes.

NON-INVASIVE BRAIN STIMULATION

Since 2000, two non-invasive brain stimulation techniques have gained increased attention in neurorehabilitation; repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS). rTMS uses a coil generating rapidly fluxing magnetic fields; applying high frequencies would in turn generate suprathreshold electrical currents that depolarize cortical neurons,[45] while applying low frequencies would lead to an inhibitory effect on neurons. Specifically, high frequency rTMS can change the resting membrane potential of neurons above a certain threshold leading to an action potential. An action potential forms the basis for signal transmission between neurons. Repetition of this signal transmission may lead to enhancement of synaptic efficiency (i.e. LTP). tDCS delivers low-intensity subthreshold electric currents (1-2 mA) using two electrodes that are placed on the head (Figure 1). It modulates the excitability of cortical neurons, by changing the resting membrane potential.[46] Specifically, the positive electrode, the anode, increases the excitability under the electrode, while the negative electrode, the cathode, decreases the excitability. tDCS may enhance the chances for an action potential, however the currents are insufficient to trigger action potentials. The advantage of tDCS over rTMS is that it is relatively less expensive, user-friendly and has limited side-effects.[47] Therefore, tDCS is a potential tool in clinical practice.

Transcranial Direct Current Stimulation

The direct effect of tDCS is modulating resting membrane potentials. Studies with healthy subjects[48] and animal models[49] have shown that long-lasting tDCS effects are related to LTP processes and BDNF secretion. Furthermore, studies have reported that multiple sessions of tDCS combined with training over multiple days may enhance training effects, compared to sham-tDCS, i.e. pseudo-stimulation.[50, 51] This long-term effect of tDCS is thought to be related with the concept of consolidation, meaning that newly formed synapses, based on experiences, become more resistant to decay over time. These findings have led to an increased interest in applying tDCS in clinical popula-

tions such as people with depression, pain, but also to treat post-stroke symptoms like hemiparesis and aphasia.

Transcranial Direct Current Stimulation to treat post-stroke aphasia

The aim of tDCS in post-stroke aphasia is to enhance effects of behavioural treatment by 1) promoting LTP processes through BDNF secretion and 2) modulating an interhemispheric imbalance and facilitating activity in the LH. In 2008, the first study regarding tDCS and post-stroke chronic aphasia was published.[52] Since then, studies have mostly combined tDCS with word-finding treatment, as the majority of people with aphasia experience word-finding difficulties.

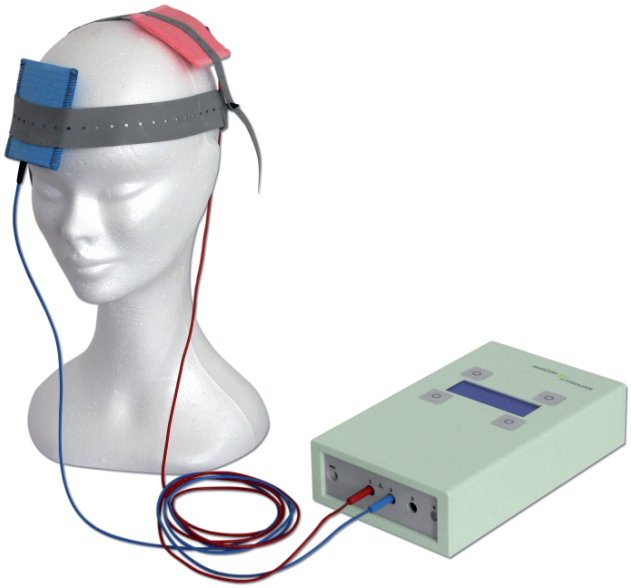

Figure 1. Transcranial Direct Current Stimulation

Different electrode configurations have been used across studies. To promote LH activity there are basically two options: the anode can be placed over LH areas or the cathode can be placed over RH areas.[53-58] tDCS has been used to target different important areas in the language system, such as the superior temporal gyrus (STG) and the inferior frontal gyrus (IFG) in the LH or in the RH. Both areas are important in the, mainly left-lateralized, process of word-finding and word production. The left STG, containing Wernicke's area, is important for access to lexical-semantic information and phonological codes.[59] The left IFG, containing Broca's area, coordinates the transformation of word representations, from the temporal cortex to the articulation stage, which is executed by the motor

cortex.[60] The left IFG is therefore an important area for phonological encoding,[59] but also for unification and binding of several linguistic processes.[61] Both the left IFG and the left STG are crucial parts of a dual-stream network model, with a dorsal frontoparietal stream supporting motor/phonological aspects of speech processing and a ventral temporofrontal stream supporting lexical-semantic aspects.[62]

Next to the interest in applying tDCS over cerebral areas, one recent case study applied tDCS over the right cerebellum.[63] Interestingly, in the last years, the cerebellum has been associated not only with motor control, but also with cognitive processing including language processing.[64] Specifically, for language processing, a crossed cerebro-cerebellar language lateralization is suggested, such that the right cerebellum is involved in language processing through cerebro-cerebellar connections with the LH.

Most studies use one configuration across participants, only few studies applied an individualized approach.[53, 55, 65] Despite differences in electrode configuration, studies report an enhanced effect of tDCS, when combined with SLT, on several language outcome measures, such as naming, comprehension and spontaneous speech.[53-55, 57, 58] However, these positive studies so far have used small samples and the consistency and reliability of tDCS effects are under discussion.[66, 67] There is a need for replication and larger trials to understand the effectiveness of tDCS. Furthermore, most studies apply tDCS in the chronic phase of aphasia, whereas it is important to investigate its effects in the sub-acute phase since most recovery takes place in this phase and most treatment is provided.

AIM OF THIS THESIS

The aim of this thesis is to improve our understanding of neuroplasticity in post-stroke aphasia, and explore whether we can facilitate this in order to optimize aphasia treatment. The primary aim is to investigate the effectiveness of tDCS in combination with SLT in post-stroke sub-acute aphasia. We set up a randomized-controlled trial (RCT) to investigate the effect of tDCS in facilitating adaptive neuroplasticity in sub-acute aphasia. In addition, the effectiveness of different tDCS electrode configurations is evaluated, namely tDCS over the left IFG, the left STG and the right cerebellum. Finally, to study inter-individual variability in neuroplasticity processes, we used 1) BDNF genotype information to compare aphasia treatment outcome between people with different BDNF genotypes and 2) neuroimaging data to evaluate individual brain activation maps, segregating areas contributing to either correct naming or naming errors.

Chapter 2 presents the study protocol for a double-blind RCT to investigate the effectiveness of tDCS in post-stroke sub-acute aphasia. The results of this RCT are presented in **chapter 3**. In **chapter 4** we compare two different electrode configurations in single therapy sessions: anodal tDCS over the left IFG and anodal tDCS over the left STG. We report the results from a group of chronic stroke patients with aphasia. **Chapter 5** presents the results of a replication study performed in healthy subjects, in which we study the effect of tDCS applied over the right cerebellum. This configuration is discussed as a potential configuration in aphasia treatment. **Chapter 6** presents a prospective cohort study to investigate the role of the BDNF genotype in the recovery of sub-acute post-stroke aphasia. **Chapter 7** of this thesis describes a neuroimaging study with chronic stroke patients, in which we studied brain activation maps related to maladaptive plasticity (i.e. incorrect naming) and compared these with brain activation maps related to adaptive plasticity (i.e. correct naming). The relative contribution of the LH and the RH related to incorrect and correct naming is evaluated. Finally, **chapter 8** presents a general discussion of the results and conclusions of this thesis.

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CHAPTER 2

Transcranial direct current stimulation in post-stroke sub-acute aphasia: study protocol for a randomized controlled trial.

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Trials. 2016 Aug 2;17:380

ABSTRACT

Background: Transcranial Direct Current Stimulation (tDCS) is a promising new technique to optimize the effect of regular Speech and Language therapy (SLT) in the context of aphasia rehabilitation. The present study focuses on the effect of tDCS provided during SLT, in the sub-acute stage after stroke. The primary aim is to evaluate the potential effect of tDCS on language functioning, specifically on word finding, as well as generalisation effects to verbal communication. The secondary aim is to evaluate its effect on social participation and quality of life, and its cost-effectiveness.

Methods: We strive to include 58 stroke patients with aphasia, enrolled in an inpatient or outpatient stroke rehabilitation program, in a multicentre double-blind randomized-controlled trial with 2 parallel groups and 6 months follow-up. Patients will participate in 2 separate intervention weeks, with a pause of 2 weeks in between, in the context of their regular aphasia rehabilitation program. The 2 intervention weeks comprise daily 45-minute sessions of word-finding therapy, combined with either anodal tDCS over the left inferior frontal gyrus (1 mA, 20 minutes; experimental condition) or sham-tDCS over the same region (control condition). The primary outcome measure is word finding. Secondary outcome measures are verbal communication, social participation, quality of life, and cost-effectiveness of the intervention.

Discussion: Our results will contribute to the discussion on whether tDCS should be implemented in regular aphasia rehabilitation programs for the sub-acute post-stroke population in terms of (cost-)effectiveness.

BACKGROUND

Aphasia is present in about 30% of patients immediately after stroke.[1] In the first weeks and months, considerable recovery may occur, however about 20% is left with chronic deficits at 6 months post-stroke.[2, 3] There is increasing support for the efficacy of Speech and Language Therapy (SLT) in order to diminish the language and communication deficits that people with aphasia encounter,[4] however, it remains a challenge to optimize the effect of aphasia therapy.

Transcranial Direct Current Stimulation (tDCS) is a promising new technique to optimize the effect of regular SLT in the context of aphasia rehabilitation.[5] It is safe and easy to apply and has limited side effects.[6] tDCS modulates cortical excitability by delivering weak electric currents to the cortex via two electrodes applied on the skull.[7] The effect of tDCS depends on the polarity of the electrodes: anodal tDCS enhances neuronal excitability while cathodal tDCS diminishes neuronal excitability. This effect is related to a change in the resting membrane potential. Anodal tDCS leads to de-polarization, increasing the chance for an action potential, and cathodal tDCS leads to hyper-polarization.[8, 9] tDCS is also related to neuroplasticity. Specifically, processes like long-term potentiation and secretion of Brain Derived Neurotrophic Factor (BDNF) are associated with tDCS application.[10] The potential benefits of tDCS applied during SLT have been described since 2008.[5, 11-17] However, these studies have some methodological limitations such as small sample size and lack of randomization.

The application of tDCS to enhance the effect of SLT is associated with the notion that tDCS may have a role in rebalancing the activity of both hemispheres post stroke. Language processing is strongly lateralized to the left hemisphere (LH), at least in right-handed healthy individuals.[18-21] After LH damage and aphasia, the right hemisphere (RH), may show increased activity. Whether this increased activity in the RH is adaptive or maladaptive, is an unresolved issue.[22-24] However, most studies indicate that, in the long term, LH perilesional recruitment is associated with better aphasia recovery, while RH recruitment is related to incomplete recovery.[25-27] In line with these observations, most studies use tDCS as a tool to promote LH perilesional recruitment.

Across studies, different electrode configurations are used to promote LH perilesional recruitment. In some studies anodal tDCS[13, 15, 16] is applied either to the left inferior frontal gyrus (Broca's area) or to the left superior temporal gyrus (Wernicke's area), while other studies use cathodal tDCS to inhibit the RH homologue areas, so as to disinhibit the LH.[14, 28] Few studies use an individual approach for electrode configurations.[11, 29] Anodal tDCS to the left inferior frontal gyrus (IFG), with the cathode placed on the contralateral supra-orbital region, is the most common configuration, which has been supported by

studies investigating this further with fMRI[30, 31] and computer modelling.[32] Predominantly, tDCS studies choose word-finding therapy as the behavioural treatment component. Irrespective of electrode configurations, studies point to an additional effect of tDCS on language functioning, when combined with SLT.[5, 11-17, 29]

Studies evaluating tDCS in sub-acute aphasia rehabilitation are limited. Evaluating the potential of tDCS in patients with sub-acute aphasia is important, as the larger proportion of language treatment for stroke patients is provided in the sub-acute phase, during the first weeks and months post stroke. During these first months, the recovery rate is highest.[33] Therefore, the aim of the present study is to investigate the effect of tDCS in sub-acute stroke patients with aphasia who are enrolled in regular stroke rehabilitation services. In line with studies applying tDCS in the chronic stage, we use the most common electrode configuration, i.e. anodal tDCS over the left IFG as compared to sham-tDCS, in combination with disorder oriented aphasia therapy, aimed at word-finding. The cathode is placed on the contralateral supra-orbital region.

Objective

The present study focuses on the effect of tDCS provided during SLT, in the sub-acute stage after stroke. The primary aim is to evaluate the effect of tDCS on language functioning. The primary outcome measure is word finding. Secondary outcome measures are verbal communication, social participation, quality of life, and cost-effectiveness of the intervention.

METHODS

Study design and procedure

The study is a multicentre double-blind randomized-controlled trial with 2 parallel groups and 6 months follow-up. Patients will participate in 2 separate intervention weeks, with a pause of 2 weeks in between, in the context of regular aphasia rehabilitation (Figure 1). During each intervention week, regular SLT sessions are replaced by daily 45-minute sessions of word-finding therapy, combined with either anodal tDCS over the left IFG (1 mA, 20 minutes; experimental condition) or sham-tDCS over the same region (control condition). The cathode is placed on the contralateral supra-orbital region. To our knowledge, a parallel design with 2 separate intervention weeks has not been used before in the tDCS literature. This design allows measurements before and after each intervention week, thus providing information on the recovery pattern over time within one subject.

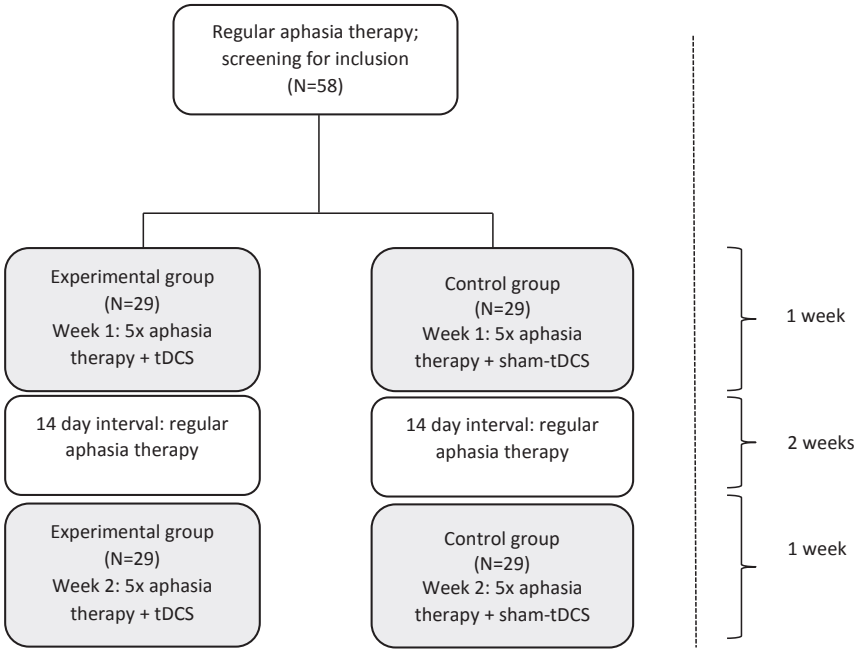

Figure 1. Study design with two separate intervention weeks.

All other therapies in the participant's stroke rehabilitation program, such as physical therapy or occupational therapy remain unchanged and are offered following the stroke rehabilitation protocol of each participating rehabilitation centre.

Setting and study population

Stroke patients with aphasia, who are receiving regular aphasia therapy, will be screened for eligibility and start the intervention between 3 weeks and 3 months after stroke. These patients are enrolled in regular stroke rehabilitation (inpatient and outpatient services) in 4 rehabilitation centres in the Netherlands: Rijndam Rehabilitation (Rotterdam), Libra Rehabilitation (Tilburg and Eindhoven), Revant Rehabilitation (Breda) and De Hoogstraat Rehabilitation (Utrecht). Table 1 lists the inclusion and exclusion criteria. We strive to include 58 patients, based on a power analysis (see section Data analysis). Before inclusion, all participants need to sign the informed consent form. Patient information is provided orally as well as in written form, with extra versions in an aphasia friendly format. This study has been approved by the Medical Ethics Committee (MEC) of the Erasmus MC, University Medical Center Rotterdam. The researcher will report Serious adverse events (SAE) to the MEC and SAEs are handled according to the WMO ('Wet Medisch-wetenschappelijk Onderzoek'), the Dutch law for medical scientific research. tDCS is known to be a safe intervention with minimal side effects.[6] Participants who develop post-stroke epileptic seizures before the end of the 4-week intervention, will

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
- Aphasia after stroke
- Less than three months post onset
- Age 18-80 years
- Near-native speaker of Dutch
- Right-handed
- Able to participate in intensive therapy
Exclusion criteria
- Subarachnoid Haemorrhage
- Prior stroke resulting in aphasia
- Brain surgery in the past
- Epileptic activity in the past 12 months
- Premorbid (suspected) dementia
- Premorbid psychiatric disease affecting communication (for example personality disorder)
- Excessive use of alcohol or drugs
- Pacemaker
- Severe non-linguistic cognitive disturbances impeding language therapy
- Global aphasia, defined as Shortened Token Test < 9[34] and score 0 on the Aphasia Severity Rating Scale[35]
- Severe Wernicke's aphasia, defined as Shortened Token Test < 9 and score 0-1 on the Aphasia Severity Rating Scale
- Residual aphasia, defined as Shortened Token Test > 28 and score 4-5 on the Aphasia Severity Rating Scale and Boston Naming Test > 150[36]

be withdrawn from the intervention, but not from the study; all assessments will be completed (intention-to-treat analysis).

Randomization and blinding

Randomization is stratified per centre of inclusion. To randomize participants to the experimental or control condition, we use a list of 5-number codes, provided by the manufacturer of the stimulation device. Half of these codes activate the device to deliver anodal tDCS (experimental condition) and half of these codes deliver sham-tDCS (control condition). Codes are block randomized with a block size of four on the basis of a computer generated sequence and then concealed in consecutively numbered, sealed, opaque envelopes. The envelope is opened at the start of the first intervention session. The participant's unique 5-number code is used to start the tDCS device, which then provides either real stimulation or sham as related to the code. The randomization and the preparation of the envelopes is done by a researcher (MH) of our research team, who is not involved in assessments and training of the patient. The key to the 5-number codes is also kept by this researcher (MH). Consequently, the participants, their SLTs and the trial coordinator are blinded to treatment condition.

Intervention

In each intervention week, regular SLT sessions are replaced by daily 45-minute sessions of word-finding therapy, combined with either anodal tDCS over the left IFG (1 mA, 20 minutes; experimental condition) or sham-tDCS over the same region (control condition). Therapy is provided by SLTs of the participating centres. The cathode is placed on the contralateral supra-orbital region. The intensity of 1 mA tDCS for 20 minutes and the frequency of 5 sessions per week, is in line with most chronic aphasia studies.[11, 13-16] tDCS is combined with word-finding therapy, because most people with aphasia have word-finding difficulties.[37] The word-finding therapy protocol is based on the Cueing Hierarchy Therapy.[38] The participant's task is to name a picture and, based on the protocol, the therapist uses cueing techniques to help the participant to retrieve and produce the target word correctly. The cue of low stimulus power is presented first, followed by increasingly powerful cues until the correct word is retrieved and produced. Basically, the following cueing hierarchy is used: 1) 'What is this?'(e.g. show picture of a tree), 2) 'Can you write the word down?', 3) Graphemic cueing (e.g. provide the number of letters), 4) Phonological cueing (e.g. provide the first sound, /t/), 5) Semantic associations (e.g. 'can you tell where you can find these'), 6) Therapist says the word (e.g. 'tree'), 7) Repetition of the target word. As the relative power of the cues differs across participants with aphasia, the exact cueing hierarchy is personalized. For each picture, even if the picture is named without cues, the participant is encouraged to write or copy the correct word form or, in case of inability to write, to perform an anagram task. The rationale for incorporating production of the written word, is the evidence that activating the written word has a beneficial effect on retrieving spoken words.[39]

To ensure relevance of the training material for each participant, stimuli are selected on the basis of individual naming performance at baseline, using the European Data Bank (EDB) for oral picture naming.[40] The first 68 items the participant is unable to name correctly within 20 s are selected. These items are divided in two sets of 34 items, matched for word length and word frequency: a therapy set, trained during the word-finding therapy, and a control set, to evaluate generalization effects to untrained items. In the first session 10 items are trained. Then, during each session new items are added, with 8 new items in the second session; 6 new items in the third and fourth session, and 4 new items in the final session. For the second intervention week a new training set is selected in the same way.

tDCS

The DC Stimulator PLUS (produced by Eldith), certified as a medical device, class IIa, by the European Union Notified Body 0118 (CE 118), is used in the authorised form. Two electrodes (5x7 cm) are placed on the head and fixed with elastic tape; electrode place-

ment is guided by the international 10-10 EEG system and previous studies.[15, 41, 42] The anode is placed on the left IFG, localised as F5, and the cathode is placed on the contralateral supra-orbital region, localised as Fp2. Participants in the experimental condition receive active stimulation of 1 mA during 20 minutes. The stimulation is automatically activated with a fade in of 15 s and after 20 minutes, the stimulation is automatically deactivated, with a fade out of 15 s. Participants in the control condition receive inactive stimulation (sham-tDCS), i.e. at first the stimulation is automatically activated with a fade in of 15 s, and then the stimulation is deactivated after 30 s, with a fade out of 15 s. Both the patient and the therapist are blinded for stimulation condition. The electrodes are not removed until completion of the 45-minute therapy session.

Measurement instruments

Table 2 gives an overview of the measurement instruments being used. The primary outcome measure is the score on the Boston Naming Test (BNT[36]), to assess picture-naming. Secondary outcome measures are chosen to evaluate generalisation of treatment effects to verbal communication: the Aphasia Severity Rating Scale (ASRS[35]) to assess spontaneous speech and the Amsterdam Nijmegen Everyday Language Test (ANELT[43]) as a measure for verbal communication in everyday life. Other secondary outcome measures are chosen to evaluate quality of life (EuroQol-5D[44]; Stroke and Aphasia Quality Of Life questionnaire[45, 46]), social participation (Community Integration Questionnaire[47]), and cost-effectiveness (Cost Analysis Questionnaire[48-50]).

Table 2. Measurement instruments

Language and communication tests
- Boston Naming Test (BNT[36])
- Aphasia Severity Rating Scale (ASRS[35])
- Amsterdam Nijmegen Everyday Language Test (ANELT[43])
- Shortened Token Test[34]
Quality of life questionnaires
- EuroQol-5D (EQ-5D[44])
- Stroke and Aphasia Quality Of Life questionnaire (SAQOL[45, 46])
Other tests
- Community Integration Questionnaire (CIQ[47])
- Cost Analysis Questionnaire[48-50]
- Barthel index[51]
- Edinburgh Handedness Inventory
- Wong-Baker Faces pain rating scale[52]

The primary outcome measure BNT, is assessed before and after each intervention week (T1, T2, T3, T4) and at 6 months follow-up (T5); see Figure 2. The secondary outcome measures are assessed before the first intervention week and after the second intervention week (T1, T4), and at 6 months (T5). The EuroQol-5D (EQ-5D) and the Cost Analysis Questionnaire are used to evaluate cost-effectiveness during the 4-week intervention period, and during the follow-up period.

Baseline assessments (T1) include handedness (Edinburgh Handedness Inventory), aphasia severity (Shortened Token Test[34]), and overall functioning (Barthel index[51]). To register potential adverse effects, participants are asked to rate their discomfort immediately after each therapy session, on the Wong-Baker Faces pain rating scale, a visual analogue scale designed for patients with limited verbal skills.[52]

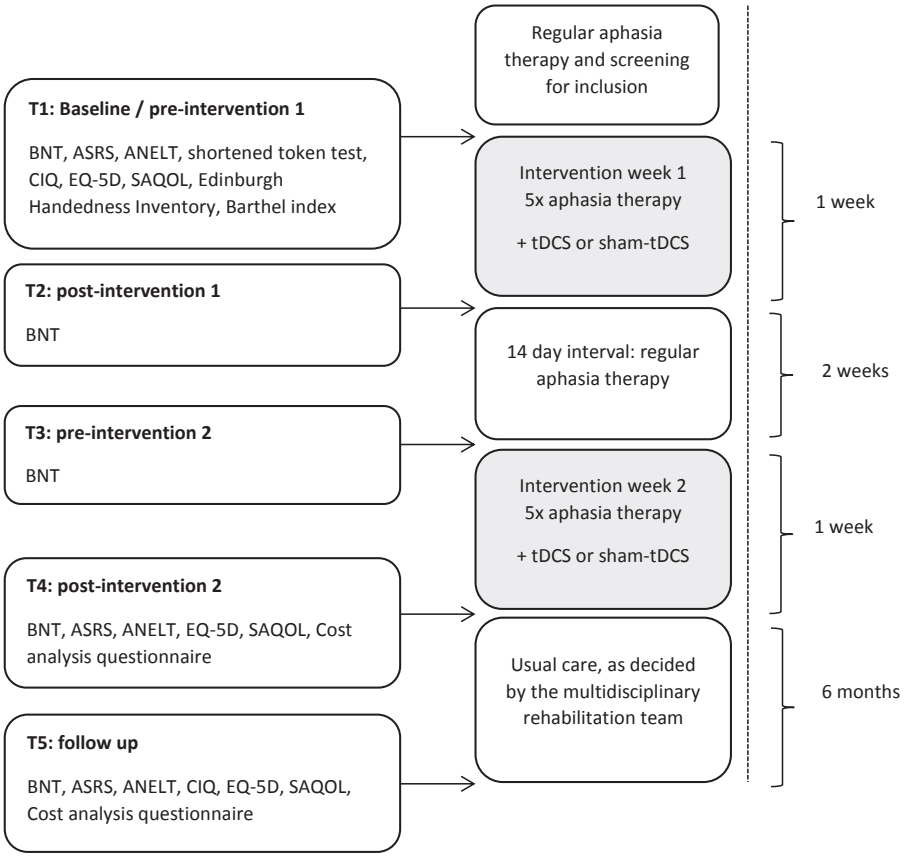

Figure 2. Measurement instruments and test moments.

Sample size

The power calculation is based on the results of a randomized-controlled trial from Baker et al.[11] including stroke patients in the chronic phase. In this study the group of aphasia patients trained with tDCS improved 2.1 points more than a sham-control group on a picture-naming test. Cohen's d effect size was 0.22, which is equal to a Cohen's f of 0.11. For the present study we calculated that, using a study design with 2 groups and 4 repeated measurements, a within-patient correlation of 0.75, an alpha of 0.05, a power of 0.80 and a Cohen's f effect size of 0.11, we need a total group of 58 patients (29 patients in each treatment arm).

Data analysis

Once randomized, each patient will be analysed in the group he/she was assigned to, independent of potential drop-out or compliance to the protocol, according to the intention-to-treat principle. Potential baseline differences between the groups will be tested using independent T-tests for continuous variables, the Mann-Whitney U test for ordinal variables, and Chi-square tests for categorical variables.

Outcomes of the measures over time will be compared for the experimental condition vs the control condition, using repeated measurements analysis. This analysis takes into account the correlation of repeated measurements within the same patients and it can handle missing data, assuming that data are missing at random. The dependent variable is the outcome measure and the independent variables are time and group assignment and the interaction between these variables. In these analyses, adjustments can be made for potentially confounding variables that could be unequally distributed over the groups despite the randomization procedure.

To evaluate cost-effectiveness, direct (para-)medical costs and the total costs of all separate treatments by health care providers during the intervention period will be summed, as well as the costs of the facilities and materials used for these treatments. In addition, the non-medical costs, such as productivity loss, will be calculated. The incremental cost effectiveness ratio will be calculated by dividing the difference in total costs by the difference in Quality-adjusted life years (QALYs), based on the EQ-5D. A net health-benefit analysis will be used to relate the costs to the benefit. We assume that the economic value of 1 life year in good health amounts to € 25.000-50.000. The economic evaluation will be performed following the Dutch guidelines.[53]

DISCUSSION

The present study focuses on the effect of tDCS provided during SLT, in the sub-acute stage after stroke. The primary aim is to evaluate the potential effect of tDCS on language functioning, specifically on word finding, as well as generalisation effects to verbal communication. The secondary aim is to evaluate its effect on social participation and quality of life, and to evaluate cost-effectiveness of this intervention.

In line with studies applying tDCS in the chronic stage, we use the most common electrode configuration, i.e. anodal tDCS over the left IFG as compared to sham-tDCS, in combination with disorder oriented aphasia therapy, aimed at word-finding. The application of tDCS, 1 mA for 20 minutes, and the frequency is also chosen in line with most chronic studies, although the discussion of what may be the optimal electrode configuration and what is the optimal stimulation intensity and frequency, is still ongoing. Regarding the optimal electrode configuration, individual factors such as lesion size and the relative contribution of the RH and the LH and its relation to aphasia recovery, may lead to individual variability in response to tDCS. However, recent fMRI and computer modelling studies find that applying anodal tDCS on the left IFG,[30-32] may be a suitable approach.

We expect that tDCS will enhance speed of language recovery, resulting in improved communication, quality of life and participation – associated with decreased rehabilitation consumption and cost reduction. If we find that tDCS enhances the effect of SLT in an early phase provided that adverse effects are limited at this stage post stroke, and if it is found to be cost-effective, tDCS may be implemented in regular aphasia rehabilitation programs for the sub-acute post-stroke population.

Abbreviations

ANELT: Amsterdam Nijmegen Everyday Language Test
ASRS: Aphasia Severity Rating Scale
BDNF: Brain Derived Neurotrophic Factor
BNT: Boston Naming Test
CIQ: Communication Integration Questionnaire
EDB: European Data Bank
EQ-5D: EuroQol-5D
IFG: Inferior Frontal Gyrus
LH: left hemisphere
QALYs: Quality-Adjusted Life Years
RH: right hemisphere
SAQOL: Stroke and Aphasia Quality Of Life
SLT: Speech and Language Therapy
tDCS: Transcranial Direct Current Stimulation

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CHAPTER 3

Transcranial Direct Current Stimulation does not improve language outcome in sub-acute post-stroke aphasia.

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ABSTRACT

Background and purpose: Transcranial Direct Current Stimulation (tDCS) is reported to enhance the effect of aphasia therapy in chronic stroke patients. However, little is known about the effect of online tDCS (i.e. simultaneous aphasia treatment) in the sub-acute phase. The aim of this study is to investigate the effect of online tDCS in sub-acute post-stroke aphasia.

Methods: In this multi-center randomized-controlled trial, we included patients with sub-acute post-stroke aphasia (<3 months post-stroke), who were enrolled in a stroke rehabilitation program. Patients participated in two separate intervention weeks, with a pause of two weeks in between. In each intervention week, participants received daily 45-minute word-finding therapy, combined with either anodal tDCS over the left inferior frontal gyrus (1 mA, 20 minutes; experimental group) or sham-tDCS over the same region (control group). The primary outcome measure was the Boston Naming Test (BNT), assessed at baseline, directly after each intervention week and at 6 months follow-up. Secondary outcome measures included naming performance for trained and untrained picture items, and tests/questionnaires to assess verbal communication, quality of life and participation. Data were analyzed with Generalized Estimation Equations.

Results: Fifty-eight patients participated, 40 men, mean age 58.9 years (SD:9.9), time post-stroke 6.7 weeks (SD:2.6). Both the experimental (n=26) and the control group (n=32) improved on the BNT, with no significant differences between groups. Also for the other outcome measures, no significant differences were found.

Conclusion: The results of the present study do not support an effect of online tDCS in sub-acute post-stroke aphasia.

INTRODUCTION

Aphasia is a language impairment which is present in about one-third of patients immediately after stroke.[1, 2] On a neural level, aphasia recovery has been described as a dynamic process. Saur et al.[3] reported increased left hemisphere (LH) activity from 4-12 months post stroke related with improved language functioning. Furthermore, several studies demonstrated that therapy-induced recovery is correlated with increased LH activity.[4-6] It is therefore assumed that LH recruitment is related with a good aphasia outcome.

In combination with multiple sessions of Speech and Language Therapy (SLT), transcranial Direct Current Stimulation (tDCS)[7-9] or repetitive Transcranial Magnetic Stimulation (rTMS)[10, 11] may improve aphasia recovery. These two non-invasive brain stimulation techniques would enhance LH recruitment and optimize the effect of SLT.[12] The advantage of tDCS over rTMS, is that it is less expensive, user-friendly and reported to be safe, with limited side-effects.[13] Therefore tDCS is a promising technique in clinical rehabilitation.

With tDCS a small current of 1-2 mA is applied; the anodal electrode enhances cortical excitability, while the cathodal electrode decreases cortical excitability.[14] It is suggested that tDCS may enhance learning through long term potentiation (LTP), i.e. long-lasting synaptic plasticity.[15, 16] For these long term processes to take place, ongoing synaptic activation is necessary,[15] and therefore tDCS is usually combined with training or treatment, which is called online tDCS.

The effect of online tDCS has mostly been studied in chronic aphasia, i.e. around 6-12 months post-stroke. These studies included small samples and used different electrode configurations.[7, 17, 18] A target of interest is the left inferior frontal gyrus (left-IFG); which is considered to be crucial for language processing. Anodal tDCS applied over this region leads to enhanced language performance in healthy subjects[19, 20] and furthermore, in chronic post-stroke aphasia, this tDCS application leads to increased use of nouns, verbs, and linguistic connectives in spontaneous speech.[7, 21]

A recent meta-analysis regarding tDCS and aphasia therapy studies, emphasized the lack of randomized clinical trials (RCTs), and the lack of studies including outcome measures for functional communication or studying long-term effects.[22] Further, it is important to investigate the effect of tDCS not only in the chronic phase, but also earlier, in the sub-acute phase (from 3 weeks to 6 months). Most recovery is observed in the first 3 months[23, 24] and treatment effects are expected to be relatively large in this period.[25] Therefore, studying the potential effect of tDCS to enhance recovery in the early stage is clinically of interest. To our knowledge, two sub-acute tDCS studies have been reported;

one study reported enhanced improvement of auditory comprehension[26] in patients with global aphasia (2-4 weeks post-stroke) and a second study reported no effect on naming[8] in a more heterogeneous group of aphasia patients (2-27 weeks post-stroke). The latter study applied tDCS offline, without simultaneous treatment. In an earlier study with chronic patients, offline tDCS did not lead to enhanced language performance (i.e. naming) compared to sham.[27]

The aim of the present study is to investigate the effect of online tDCS in a sub-acute post-stroke rehabilitation population. We included participants within three months post-stroke and performed a multi-center RCT with two parallel groups and six months follow-up. Aphasia therapy aimed to train word-finding was combined with either active tDCS or sham-tDCS over the left-IFG. The primary outcome measure was picture naming. We also included outcome measures assessing verbal communication, quality of life and participation. We hypothesized that participants in the active tDCS group show improved recovery in terms of word-finding, and that this in turn would lead to improvement in verbal communication, quality of life and participation.

1. MATERIALS AND METHODS

1.1 Design

We performed a multi-center RCT. Between three weeks and three months post-stroke, people with aphasia participated in two intervention weeks separated by two weeks. These intervention weeks were incorporated in regular aphasia treatment, in an interdisciplinary stroke rehabilitation program. Thus, before and after the intervention, and in the two-week pause, participants received usual care. In each intervention week, participants received daily sessions of word-finding therapy (45-minutes) combined with either anodal tDCS over the left-IFG (experimental condition) or sham-tDCS over the same region (control condition).

1.2 Power analysis

The power calculation was based on the results of Baker et al.'s study[17] of patients with chronic aphasia. In this within-subject cross-over study, participants improved 2.1 points more on a picture naming test during a 1-week treatment combined with tDCS compared to a 1-week treatment combined with sham. Cohen's d effect size was 0.22, which is equal to a Cohen's f of 0.11. We calculated that for our design, with two groups and four repeated measurements, a within-patient correlation of 0.75, an alpha of 0.05, a power of 0.80 and a Cohen's f effect size of 0.11, a total number of 58 patients was needed (29 patients in each treatment arm).

1.3 Participants

From March 2014 to October 2017 patients were screened at four rehabilitation centers in the Netherlands: Rijndam Rehabilitation, Revant Rehabilitation, Libra Rehabilitation and De Hoogstraat. Inclusion and exclusion criteria are presented in Table 1. Patient information was provided both orally and in a written form, with an extra version in an aphasia-friendly format. All participants signed informed consent. This study was approved by the Medical Ethics Committee of the Erasmus MC, University Medical Center Rotterdam.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
- Aphasia after stroke
- Less than three months post onset
- Age 18-80 years
- Near-native speaker of Dutch
- Right-handed
- Able to participate in intensive therapy
Exclusion criteria
- Subarachnoid Haemorrhage
- Prior stroke resulting in aphasia
- Brain surgery in the past
- Epileptic activity in the past 12 months
- Premorbid (suspected) dementia
- Premorbid psychiatric disease affecting communication (for example personality disorder)
- Excessive use of alcohol or drugs
- Pacemaker
- Severe non-linguistic cognitive disturbances impeding language therapy
- Global aphasia, defined as Shortened Token Test < 9[28] and score 0 on the Aphasia Severity Rating Scale[29]
- Severe Wernicke's aphasia, defined as Shortened Token Test < 9 and score 0-1 on the Aphasia Severity Rating Scale
- Residual aphasia, defined as Shortened Token Test > 28 and score 4-5 on the Aphasia Severity Rating Scale and Boston Naming Test > 150[30]

1.4 Randomization and blinding procedure

After the baseline assessments, participants were randomized into the experimental group or control group. Randomization was stratified for rehabilitation center, on the basis of a random block design (block size=4). One of the authors (MHK, epidemiologist), not involved in selecting, testing, or treating participants, performed the randomization using an online random number generator. The random numbers were combined with 5-number codes from the tDCS manual for active or sham-tDCS. These codes were

concealed in opaque envelopes; a unique code was used for each individual and was opened at the first therapy session. This code was entered into the tDCS device to start a pre-set program, either active tDCS or sham. In this way, participants, speech and language therapists (SLT), the research coordinator, and research (test) assistants were blinded for tDCS condition.

1.5 Treatment: tDCS and word-finding training

We used the DC Stimulator PLUS (produced by Eldith) in the authorized form. This device is certified as a medical device, class IIa, by the European Union Notified Body 0118 (CE 118). Before starting each 45-minutes session of word-finding therapy, two electrodes (5x7 cm) with saline-soaked sponges were placed on the head, using elastic tape. Electrode placement was guided by the international 10-10 Electroencephalogram (EEG) system; the F5-EEG position was used for the anode position over the left-IFG[31] and the FP2-EEG position was used for the cathode position over the right hemisphere (RH) supra-orbital region. In the active tDCS condition, a current of 1 mA automatically faded in in 15s, and after 20 minutes the current faded out in 15s, whereas in sham-tDCS, a current of 1 mA faded in in 15s and after 30s, the current faded out in 15s.

Before each intervention week, pictures from the European Data Bank for oral picture naming were presented and the first 68 items that the participant could not name orally within 20s were selected.[32] From these items, 34 were selected for training (i.e. trained items) and 34 were used to assess generalization of the therapy to untrained items; sets for trained and untrained items were matched for word length and word frequency (i.e. frequency with which a word occurs). Participants' SLTs were trained to use a hierarchical cueing program for word-finding.[33] The cue of the lowest stimulus power was presented first, followed by increasingly powerful cues until the participant was able to retrieve and produce the correct word. More detailed information about the word-finding treatment is provided elsewhere.[34] To register potential adverse effects, participants were asked to rate their discomfort immediately after each therapy session on the Wong-Baker Faces pain rating scale (WB scale), a visual analog scale designed for people with limited verbal skills.

1.6 Assessments

1.6.1. Baseline measures

Beside demographic data, we collected data on handedness (Edinburgh Handedness Inventory)[35], severity of aphasia (shortened form of the token test; STT)[36], and overall functioning (Barthel Index)[37] at baseline.

1.6.2. Primary and secondary language measures

The 60-item Boston Naming Test (BNT)[38], assessing word-finding, was the primary outcome measure. In the Dutch version, item 57 ('trellis') is not included, because of its low naming agreement in a Dutch norm group.[39] This test was administered before and after each intervention week (T1, T2, T3, T4) and at 6 months follow-up (T5).

Secondary language measures included naming performance for the 34 trained and 34 untrained items, which was assessed after each intervention week (T2 and T4). Verbal communication was assessed with the Aphasia Severity Rating Scale (ASRS)[40] and the Amsterdam Nijmegen Everyday Language Test (ANELT)[41]. The ASRS is a 6-point rating scale to judge communicative ability in a semi-structured interview. The ANELT is a test with 10 possible everyday scenarios in which the participants' response is scored on a 5-point scale. The ASRS and ANELT were administered before the first intervention week (T1), after the second intervention week (T4), and at 6 months follow-up (T5).

For all naming tasks, responses were audio-recorded and scored off-line by a trained test assistant, who was blinded for tDCS condition. A response was scored as either correct, if the participant was able to produce the target word or a synonym within 20s, or incorrect. The interview (ASRS) and ANELT were audio-recorded and were scored offline by experienced clinical linguists, which were blinded both for tDCS condition and test moment.

1.6.3. Tertiary outcome measures: quality of life and participation

Quality of life was measured with the Stroke and Aphasia Quality Of Life scale (SAQOL-39)[42]. The SAQOL-39 is a 39-item questionnaire covering 4 domains: physical, psychosocial, communication, and energy. Each item can be scored from 1-5, higher scores indicate higher quality of life. All items ask for recent experiences in the past week, for example 'During the past week, how much trouble did you have with speaking?'. The SAQOL-39 was assessed at T1, T4 and T5.

Participation was assessed with the Community Integration Questionnaire (CIQ).[43] This is a 15-item questionnaire covering three domains: Home integration, Social integration and Integration in Productive activities. Each item can be scored from 0-2, higher scores indicate better integration. The CIQ was administered at T5; all items ask for experiences in the past 6 months. For example, 'In the last 6 months, who usually prepared meals in your household?'

1.7 Data analysis

Baseline differences between the experimental and control group were tested by independent t-tests, chi-square tests and Mann-Whitney U tests, as appropriate. Data from the language measures and quality of life questionnaire, were analyzed using a Generalized Estimation Equation (GEE) model on an intention-to-treat basis. We chose the GEE because some of the outcome measures were not normally distributed; the GEE is a semiparametric method that does not depend largely on the specification of the underlying distribution of the outcomes. As part of this model, a correlation matrix is estimated that represents the within-subject dependencies. Fixed factors in the model were Group (experimental or control) and Time (T1, T2, T3, T4, T5) and the interaction between these fixed factors (Group x Time). The outcome measures at each time point were included as the dependent variable. GEE assumes that data are missing at random. Data from the participation questionnaire at T5 was analyzed with an independent t-test. $P<0.05$ was considered statistically significant.

2. RESULTS

Fifty-eight participants participated of which 26 were allocated to the experimental group and 32 to the control group. Two patients dropped out after the first week; one participant from the experimental group stopped with inpatient rehabilitation, and one in the sham group underwent brain surgery (tDCS could not be continued conform the exclusion criteria). Fifty-four participants (93.1%) completed follow-up. Figure 1 presents a flow-diagram.

Table 2 presents demographic characteristics of the study sample. The mean age was 58.9 (SD:10.0) years and 69% were men. Participants started tDCS treatment at 6.7 (SD:2.6) weeks post-stroke. No significant differences were found between groups. Table 3 presents baseline scores for the outcome measures.

Participants tolerated the treatment well. WB-scores ranged from 0-2, with a median of 0 (IQR:0-0). Sixty-nine percent reported a score of 0 (“no pain”); 31% reported a score of 1 or 2 (1=”very little pain”, 2: “little pain”), 44% of these participants received active stimulation. There was no significant difference in pain rating scores between groups ($p=0.725$). Reported side effects included: headache (n=1, experimental group, 1 out of 10 sessions) and skin irritability (n=2, experimental group, 3 out of 10 sessions). No other adverse events were reported.

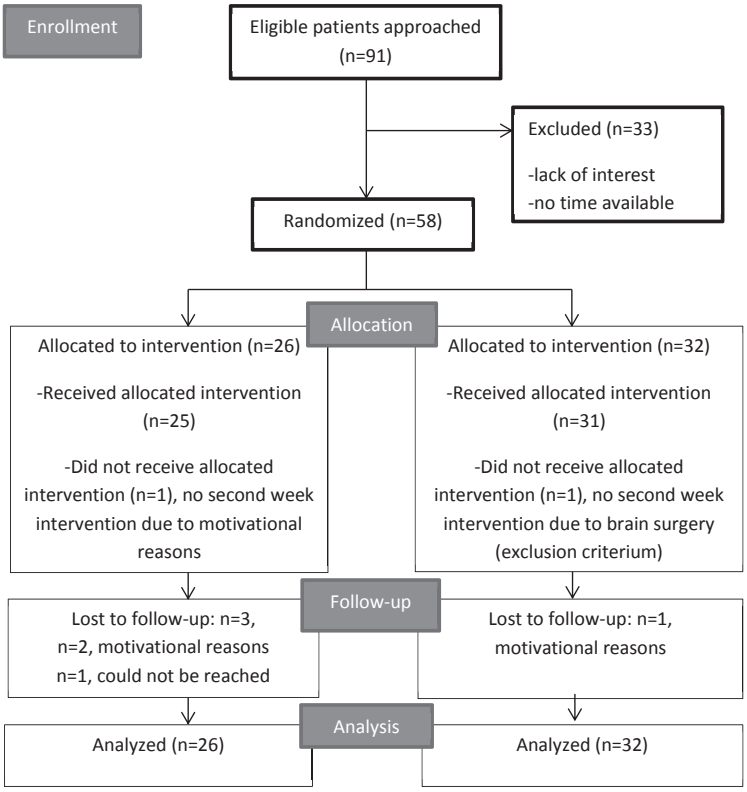

Figure 1. Flow diagram.

2.1 Language measures

2.1.1 Primary outcome measure: Boston naming test

At baseline, there were no significant differences in naming (BNT) between groups (Table 3). Both groups scored significantly better on the BNT over time ($p<0.001$). BNT scores increased from T1 (25.1, SE:2.1) to T2 (28.6, SE:2.1), to T3 (30.8, SE:2.2), to T4 (31.3, SE:2.2), and to T5 (37.2, SE:1.9). All improvements were significant, except for the second intervention week (T3-T4). No significant effect was found of active tDCS compared to sham-tDCS ($p=0.994$) over the intervention period or follow-up (Figure 2).

Table 2. Demographic characteristics for each group.

	Experimental group (n=26)	Control group (n=32)	p-value
Age, years, mean (SD)	57.9 (9.6)	59.7 (10.3)	0.515
Gender, male (%)	18 (69.2)	22 (68.8)	0.969
Edinburgh Handedness, mean (SD)	0.99 (0.05)	0.97 (0.08)	0.553
Education group, n (%)			0.826
Low education			
(Verhage 1-4)	8 (13.8)	9 (15.5)	
High education			
(Verhage 5-7)	18 (31.0)	23 (39.7)	
Education, years, mean (SD)	12.2 (3.4)	13.1 (3.2)	0.277
Paresis/paralysis, yes, n (%)	16 (61.5)	12 (37.5)	0.068
Barthel Index at admission, mean (SD)*	13.1 (7.0)	16.4 (4.7)	0.113
Stroke type, n (%)			0.123
ischemic	20 (76.9)	30 (93.8)	
hemorrhagic	6 (23.1)	2 (6.3)	
Time post stroke, weeks, mean (SD)	6.3 (2.3)	7.1 (2.9)	0.220
Premorbid stroke, yes, n (%)	1 (3.8)	3 (9.4)	0.156
Aphasia severity according to Shortened tokentest (STT), mean (SD)	18.8 (7.9)	19.1 (9.0)	0.917
Aphasia type, n (%)			0.945
Fluent	13	17	
Nonfluent	9	11	
Mixed	4	4	

*Missing data Barthel Index, in the experimental group n=10 and in the control group n=8

Table 3. Baseline data of the outcome measures

	Experimental group	Control group	p-value
Boston Naming Test[a]	23.9 (16.5)	27.7 (14.3)	0.348
Aphasia Severity rating scale[b]	2.5 (1.2)	2.7 (1.1)	0.496
Amsterdam-Nijmegen Everyday Language Test[c]	29.5 (13.4)	29.6 (12.7)	0.992
Stroke and Aphasia Quality Of Life scale[d]	3.6 (0.8)	3.9 (0.7)	0.184

[a] missing data, sham group n=1
[b] missing data, sham group n=1
[c] missing data, experimental group n=1 and sham group n=5
[d] missing data, sham group n=2

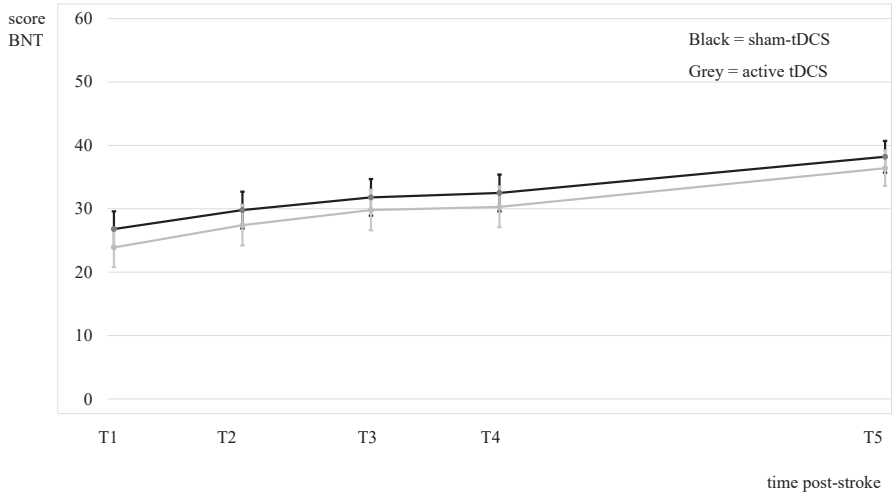

Figure 2. Score on the Boston Naming Test over time for the experimental group (active tDCS), presented in grey, and the control group (sham-tDCS), presented in black.

2.1.2. Naming trained and untrained items

For the trained items, participants correctly named 66.3% (SE:3.9) of the items after the first intervention week (T2) and 70.8% (SE:3.5) after the second intervention week (T4). The performance at T4 was significantly higher than at T2 (effect of time: p=0.007). For the untrained items, participants correctly named 38.2% (SE:2.9) of the items at T2 and 34.2% (SE:2.5) at T4; there was no statistically significant difference in performance at T2 compared to T4 (p=0.063). No significant effect was found of active tDCS compared to sham-tDCS over the intervention period, neither for trained items (p=0.616) nor for untrained items (p=0.404).

2.1.3. Verbal communication: ASRS and ANELT

Both ASRS and ANELT scores showed a significant improvement over time in both groups (p<0.001). The performance on the ASRS improved significantly from 2.6 (SE:0.2) at T1 to 2.9 (SE:0.2) at T4 and to 3.6 (SE:0.2) at T5. The performance on the ANELT improved significantly from 29.1 (SE:1.7) at T1 to 32.5 (SE:1.6) at T4 and 38.4 (SE:1.4) at T5. No significant effect was found of active tDCS compared to sham-tDCS over the intervention period or follow-up, neither on the ASRS (p=0.828) nor on the ANELT (p=0.983).

2.2 Quality of life

The SAQOL-39 score significantly improved over time in the total group (p<0.001). Quality of life significantly improved from 3.7 (SE:0.1) at T1 to 3.9 (SE:0.1) at T4, and to 4.2 (SE:0.1) at T5. No significant effect was found of active tDCS compared to sham-tDCS (p=0.203) over the intervention period or follow-up.

2.3 Participation

For the CIQ total score at T5, 6.9% of the data were missing. The mean score in the experimental group was 14.6 (SD:6.5) and in the control group 15.9 (SD:5.9); this difference was not significant (p=0.433).

DISCUSSION

The aim of this multi-center double-blinded RCT was to investigate the effect of online tDCS in the sub-acute phase post-stroke. Over time, both the experimental group and the control group improved on the BNT, however, this improvement did not significantly differ between groups. In addition, no significant differences between groups were found for the personalized sets of trained/untrained items of the two intervention weeks and on the verbal communication tests. Therefore, this study did not show an effect of online tDCS in sub-acute aphasia, not at the impairment level, in naming picture items and trained/untrained items, not on verbal communication, quality of life and participation. Also we found no adverse effects of tDCS.

These results are in line with the results of Polanowska et al.,[8] who also failed to show significant effects of tDCS in sub-acute aphasia using an offline treatment paradigm. However, studies in the chronic phase post stroke showing an effect of tDCS, used an online treatment paradigm.[7, 17, 18] Polanowska et al.[8] hypothesized that as spontaneous recovery is high in the sub-acute phase, an effect of tDCS might be difficult to achieve. This suggests that phase rather than (offline or online) treatment paradigm predicts efficacy of tDCS. This is in line with a recent meta-analysis that reported a small and significant effect of tDCS in the chronic phase, while the effect of tDCS in the sub-acute phase was small and not significant.[12]

Interestingly, the same meta-analysis reported that rTMS may have an effect in the sub-acute phase. Further, in the chronic phase, small but significant effects were reported both for rTMS and tDCS with a slightly larger effect of rTMS compared to tDCS. This suggests that rTMS is more effective than tDCS in both the sub-acute and chronic phase. Why would this be the case? First of all, rTMS elicits a stronger electric field compared to tDCS,[13] increasing the chance of generating an action potential, followed by neuroplastic reactions. Second, localization of the rTMS coil is more precise, using neuronavigation, compared to the electrode placement of tDCS using the EEG system. Third, rTMS studies in the sub-acute phase either inhibit RH frontal areas[10, 11] or use dual rTMS[44] to simultaneously stimulate LH areas and inhibit RH areas. Inhibiting RH areas might be more effective in the sub-acute phase, perhaps because a spontaneous increase in excitability

would already be present after stroke in the LH perilesional areas surrounding the core lesion area.[45]

In this study, but also in most other studies, one predefined electrode configuration is used for all participants. However, the optimal configuration may well vary across subjects depending on aphasia type, or size/site of the stroke. For example, one study included only patients with global aphasia and reported an effect of tDCS in the sub-acute phase.[26] Moreover, even within patients, the optimal electrode configuration may vary in time. Based on the study of Saur et al.,[3] showing that time post-stroke is a critical factor to understand the dynamics of LH vs RH activation, it might be that inhibiting the RH is a suitable approach in the sub-acute phase, while enhancing the LH may be more suitable in the chronic phase.

Limitations and future research

A limitation of the study is that we do not have lesion information of all participants. Future research should explore an individual approach of tDCS. Further, as intensity and spatial precision of the electric current may determine the effect of tDCS, new techniques such as High Definition (HD)-tDCS may be promising in increasing the effectiveness of conventional tDCS.[46]

Conclusion

In this multi-center RCT including 58 participants with post-stroke sub-acute aphasia, we do not find any support for using tDCS as an adjuvant treatment to SLT aimed at word-finding.

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CHAPTER 4

Evaluation of a protocol to compare two configurations of Transcranial Direct Current Stimulation for aphasia treatment.

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ABSTRACT

Objective: To compare two configurations of Transcranial Direct Current Stimulation (tDCS) for aphasia treatment.

Design: Randomized cross-over study.

Subjects: Patients with chronic post-stroke aphasia (n=13).

Methods: tDCS was combined with word-finding therapy in three single sessions. In session 1, sham-tDCS/pseudo-stimulation was applied, and in sessions 2 and 3 two active configurations were counterbalanced: anodal tDCS over the left inferior frontal gyrus (l-IFG) or over the left posterior superior temporal gyrus (l-STG). An optimal configuration was determined per individual based on a pre-set improvement in naming trained (>20%) and untrained picture items (>10%).

Results: Overall, participants improved on trained items (median=50%; IQR=20-85) and post-treatment performance was highest in the active l-IFG condition (p=0.040). Of the 13 participants, six (46%) showed relevant improvement during active tDCS; either in the l-IFG condition (n=4;31%) or both in the l-IFG and l-STG condition (n=2;15%). On the untrained items there was no improvement (median=0%; IQR=0-0).

Conclusion: This randomized cross-over single-session protocol to determine an optimal tDCS-configuration for aphasia treatment suggests that only performance on trained items can be used as a guidance for configuration and that it is relevant for half of the patients. For this subgroup, the l-IFG configuration is the optimal choice.

INTRODUCTION

About one-third of stroke patients have aphasia, a language disorder typically caused by damage to left hemisphere (LH) regions.[1] Multiple sessions of Speech and Language Therapy (SLT) combined with Transcranial Direct Current Stimulation (tDCS) may enhance language functioning, compared to sham-tDCS (i.e. pseudo-stimulation).[2-8] With tDCS, two electrodes are placed on the outside of the head to apply a weak current of 1-2 mA to the cortical areas.[9-11] Anodal tDCS enhances neuronal excitability while cathodal tDCS diminishes neuronal excitability. As LH activation is thought to be crucial for aphasia recovery,[12, 13] most studies aim to promote LH activity by applying anodal tDCS over LH regions.

Studies mostly focus on two crucial language areas; the left inferior frontal gyrus (l-IFG) and the left posterior superior temporal gyrus (l-STG).[14, 15] Damage to the l-IFG is associated with non-fluent aphasia, which is characterized by non-fluent, sparse, dysprosodic, and agrammatic speech production.[16] Damage to the posterior l-STG is associated with fluent aphasia, which is characterized by fluent speech with phonemic and semantic paraphasias.[17] It has been reported that anodal tDCS over the l-IFG or l-STG improves language functioning, both in healthy speakers and in people with aphasia (PWA).[5, 6, 18-22]

Recent studies emphasize that the optimal electrode configuration may vary across PWA, due to factors such as severity/type of aphasia and lesion size.[2, 23-25] For example, Baker et al.[2] hypothesized that frontal stimulation may be beneficial for people with frontal damage (non-fluent aphasia), while posterior stimulation may be beneficial for people with posterior damage (fluent aphasia). Interestingly, one within-subject study applied multiple tDCS sessions in patients with non-fluent aphasia and reported an advantage of anodal tDCS over the l-IFG, compared to anodal tDCS over the l-STG and sham.[6]

In order to take into account individual variability, some studies determine an optimal electrode configuration per individual before starting with multiple tDCS sessions. Two studies used neuroimaging to guide individualized electrode placement[2, 4] and, although this may be a useful method, it is also relatively expensive, time-consuming and not applicable to all patients. Another approach is to use behavioral measures,[24, 26] which would be more feasible in day-to-day clinical practice. For example, Shah-Basak et al.[24] compared the effect of different electrode configurations within participants in single therapy sessions; improvement on naming untrained items was the outcome measure and the results showed that participants vary in their response to different electrode configurations. It is therefore suggested to develop a single-session protocol to determine an optimal configuration before starting multiple tDCS sessions.

The aim of the present study is to evaluate such a protocol to compare anodal tDCS over the l-IFG with anodal tDCS over the l-STG in patients with chronic aphasia. The two outcome measures are naming performance on both trained and untrained picture items. Interpersonal variability in response to l-IFG versus l-STG stimulation is related to the aphasia type (i.e. non-fluent versus fluent aphasia).

METHODS

Study design

In a double-blind randomized cross-over design, participants were assigned to a sequence of three therapy sessions. In each session, a 30-min word-finding therapy was combined with one of three tDCS conditions; sham-tDCS, i.e. pseudo-stimulation (session 1), or with anodal tDCS over the l-IFG or the l-STG (randomized over sessions 2 and 3). All three therapy sessions were completed in 2-4 weeks, with a minimum interval of three days between sessions. This study was approved by the Medical Ethics Committee of the Erasmus University Medical Center Rotterdam.

Participants

Participants were recruited at Rijndam Rehabilitation between February and December 2016. They were either enrolled in or had completed their stroke rehabilitation program. Additional participants were recruited through a Dutch website for therapists and PWA (www.afasienet.com). The inclusion and exclusion criteria are presented in Table 1.

Transcranial Direct Current Stimulation

We used the DC Stimulator PLUS (produced by Eldith) in the authorized form. This device is certified as a medical device, class IIa, by the European Union Notified Body 0118 (CE 118). Before starting the 30-min word-finding therapy, two electrodes (5x7 cm) were placed on the head, using elastic tape. Electrode placement was guided by the international 10-10 Electroencephalogram (EEG) system: the F5 EEG position was used for the l-IFG configuration[27] and the CP5 EEG position for the l-STG configuration.[28] The device was pre-programmed (with a unique 5-number code per participant and per session) for either sham or active stimulation (1mA). Thus, both the patient and the Speech and Language therapist (SLT; in training) were blinded for the stimulation condition.

In the first session, all patients received sham-tDCS, i.e. pseudo-stimulation. The anode was placed over the l-IFG or the l-STG (counterbalanced across participants). In this condition, stimulation was automatically activated with a fade in of 15 s and, after 30 s, the stimulation was deactivated with a fade out of 15 s. In sessions 2 and 3, patients received active tDCS; the sequence of electrode placement was randomized, with the

anode either placed over the l-IFG or the l-STG. The stimulation was automatically activated with a fade in of 15 s, and deactivated after 20 min with a fade out of 15 s. In all three conditions, the cathode was placed over the contralateral supra-orbital region (EEG position: Fp2).

Table 1. Inclusion and exclusion criteria

Inclusion criteria
- Aphasia after stroke
- Time post onset ≥ 6 months
- Age 18-80 years
- Native speaker of Dutch
- Right-handed
- Aphasia after stroke
Exclusion criteria
- Subarachnoid hemorrhage
- Prior stroke resulting in aphasia
- Brain surgery in the past
- Epileptic activity in the past 12 months
- Excessive use of alcohol or drugs
- Premorbid (suspected) dementia
- Premorbid psychiatric disease affecting communication
- Severe non-linguistic cognitive disturbances impeding language therapy
- Pacemaker
- Global aphasia, defined as Shortened Token Test < 9[29] and score 0 on the Aphasia Severity Rating Scale[30]
- Severe Wernicke's aphasia, defined as Shortened Token Test < 9 and score 0-1 on the Aphasia Severity Rating Scale
- Residual aphasia, defined as Shortened Token Test > 28 and score 4-5 on the Aphasia Severity Rating Scale and Boston Naming Test > 150[31]

Procedure

A baseline assessment was performed before inclusion to assess handedness with the Edinburgh Handedness Inventory (EHI),[32] severity of aphasia with the Short Form of the Token Test (STT),[29] and spontaneous speech with the Aphasia Severity Rating Scale (ASRS).[33] The baseline assessment was followed by the first of three therapy sessions (A, B, C). In each treatment session, we used two picture-naming tasks, one to select training items per individual (tasks A1, B1, C1), and a second task to evaluate generalization to untrained items (tasks A2, B2, C2). In total, six tasks were used, matched for word length and word frequency. Each task comprised 30 pictures depicting nouns selected from the European Data Bank.[34]

All pictures were presented on a computer screen for 5 s followed by a blank slide for 3 s (using Powerpoint) and responses were audio-recorded. A response was scored as correct when the participant was able to produce the target word (or a synonym) within 5 s, otherwise it was scored as incorrect. The first 10 incorrect responses from A1, B1, and C1 respectively, were selected for treatment, and this 'therapy set' was trained during the 30-min aphasia therapy combined with one of the three tDCS conditions. In case participants named less than 10 items incorrectly, items from an extra set were used to complete the therapy set. For the therapy, the SLT was trained to use cueing techniques to help the participant to correctly retrieve and produce the target word.[35] The cue of the lowest stimulus power was presented first, followed by increasingly powerful cues until the correct word was retrieved and produced. Details on the therapy are published elsewhere.[36] At the end of each session, the therapy set was administered (without help). The 30 pictures of the second naming task (A2, B2, C2) were presented before and after each therapy session, and results were used to study the treatment effect on untrained material. Figure 1 presents an overview of the sessions and tasks. Finally, to assess discomfort, we asked participants to fill in a Wong-Baker Faces Pain Rating scale (WB scale) after each session.[37] This is a visual analog scale ranging from 0-5, developed for individuals with limited verbal skills.

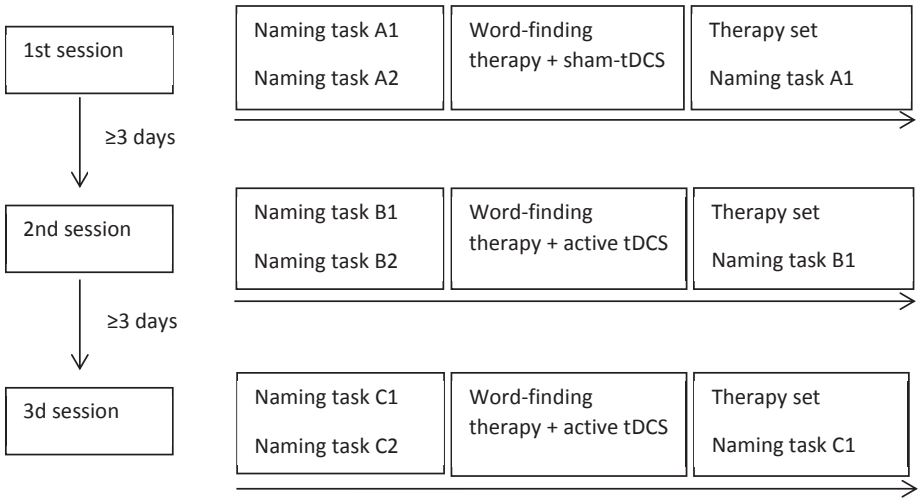

Figure 1. An overview of the three sessions and tasks.

Data analysis

All naming tasks were scored offline by a trained test assistant, who was blinded for the tDCS condition. For the untrained items, the test assistant was also blinded for pre-treatment versus post-treatment assessments. For the trained items, this was not possible because performance was only tested post-treatment; per definition, before

therapy, the percentage correct was 0%. In general, a response was scored as correct when the participant was able to produce the target word or synonym within 5 s. A pre-set list was made with synonyms, i.e. correct alternatives for the target word. In case the participant produced a synonym that was not listed as a correct alternative, the test assistant and research coordinator discussed whether (or not) it should be considered correct. If agreement could not be reached, half a point was given for the produced item. An experienced clinical linguist (WS-K) assessed the ASRS samples and classified participants' aphasia as fluent or non-fluent.

The main outcome measure was the proportion of correct responses on the therapy set (10 items) after therapy, across the three conditions: sham, l-IFG and l-STG. The secondary outcome measure was the improvement on untrained items (30 items), across the three conditions. Per condition, we calculated the delta score, defined as the proportion of correct responses post-treatment minus the proportion of correct responses pre-treatment.

To determine an optimal configuration per individual, individual response patterns across conditions were analyzed. For the trained items, we considered a proportional improvement of 20% between conditions as relevant, in line with a previous study comparing the same three tDCS conditions and using naming performance as an outcome.[22] Specifically, we considered the condition in which the performance was 20% higher than in the other two conditions as the optimal configuration for an individual. The same method was used for the untrained items, but here we used a smaller proportional difference of 10% since there is generally less improvement on untrained items.

In addition, we investigated whether, at the group level, the two configurations of interest yielded different results of naming performance after one single therapy session. Thus, we compared proportions of improvement across conditions, also taking into account the order in which the montages were applied. A Kolmogorov-Smirnov test revealed that the data were normally distributed for trained items ($D(39)=0.118$, $p=0.188$, two-tailed), but not for untrained items ($D(39)=0.233$, $p<0.001$, two-tailed). Therefore, data were analyzed with the semiparametric Generalized Estimation Equation (GEE) analysis, which takes into account that multiple measurements within patients are correlated. To study the effect of condition (sham, l-IFG, l-STG), measurement time (session 1-3) and configuration order (starting with l-IFG or l-STG in session 2), these variables were entered as fixed factors into the model, in which either the post-treatment scores of the trained items or the delta scores of the untrained items was the dependent variable. If a factor had a significant effect on the outcome, post-hoc pairwise comparisons were performed to specify the significant differences within each factor. Finally, patient discomfort rating, assessed with

the WB scale, was tested with a Mann-Whitney U-test. The level of significance (p) was 0.05 in all analyses. IBM SPSS 21 Statistics software was used for all statistical tests.

RESULTS

All participants completed the three therapy sessions. On average, the interval between sessions was 6 (SD=2.9) days (between session 1 and 2, mean=5.3 days, SD=1.8 days; between session 2 and 3, mean=6.7 days, SD=3.7 days). No side-effects were observed. All participants tolerated the treatment well; however, some participants reported that the treatment sessions were rather intensive. Overall, discomfort ratings were low and ranged from 0 to 1, with median scores of 0 for each session (IQR session 1: 0-0, session 2: 0-0, session 3: 0-0.75). Discomfort ratings were comparable across sessions; Mann-Whitney U (Friedman: $X^2(2)=1$, p=0.607).

A. Participants

A total of 13 participants were recruited (10 men; mean age=53.15, SD=10.90 years). All participants were right-handed (EHI>0.50; mean=0.96, SD=0.12) and at least 6 months post-stroke (MPO; mean=48.92, SD=48.43 months). Demographic and clinical characteristics of each participant are presented in Table 2.

Table 2. Demographic information and clinical data of the participants.

P	Sex	Age (years)	Stroke	Education (Verhage[1])	MPO	STT	Severity aphasia[2]	ASRS	Type of aphasia
1	M	39	Ischemic	7	9	14	Severe	3	Non-fluent
2	M	65	Ischemic	6	7	24.5	Moderate	3	Non-fluent
3	M	61	Ischemic	6	112	11.5	Severe	2	Fluent
4	F	69	Ischemic	5	6	7	Very severe	1	Fluent
5	M	55	Ischemic	5	31	1	Very severe	1	Non-fluent
6	F	59	Ischemic	6	15	28.5	Mild	4	Fluent
7	M	32	Ischemic	2	26	5.5	Very severe	3	Fluent
8	M	44	Hemorrhage	5	9	18.5	Moderate	4	Fluent
9	M	54	Ischemic	4	20	20.5	Moderate	1	Non-fluent
10	M	67	Ischemic	7	74	7.5	Very severe	2	Non-fluent
11	F	48	Ischemic	5	138	17.5	Moderate	1	Non-fluent
12	M	44	Ischemic	6	51	27.5	Mild	3	Fluent
13	M	54	Ischemic	6	138	9	Severe	3	Fluent

Abbreviations: P=participant ID number, M=male, F=female, MPO=months post stroke, STT=shortened form of the token test, ASRS=aphasia severity ranking scale

[1]based on Verhage Education system[38]

[2]based on STT

B. Individual response patterns

Table 3 presents the post-treatment and delta scores for trained and untrained items respectively, per individual (see the supplementary material for a table with the pre and post scores for trained and untrained items).

Table 3. Delta scores (%) on trained and untrained items per individual.

		Session 1		Session 2		Session 3	
P	Configuration order session 2 and 3	Trained	Untrained	Trained	Untrained	Trained	Untrained
1	STG-IFG	50	13.3	60	0	90	-6.6
2	IFG-STG	90	6.7	100	3.3	100	0
3	IFG-STG	60	0	65	-23.3	60	-10.0
4	STG-IFG	0	0	0	0	0	0
5	IFG-STG	20	0	0	0	10	0
6	STG-IFG	90	3.4	95	10	80	0
7	IFG-STG	70	0	100	0	50	-16.7
8	STG-IFG	20	-3.3	50	-6.7	50	0
9	STG-IFG	50	6.7	40	-3.4	70	3.3
10	IFG-STG	20	-16.7	30	-3.3	30	0
11	IFG-STG	10	3.4	30	0	0	-6.7
12	STG-IFG	100	3.3	85	-3.4	100	-10.0
13	IFG-STG	40	10.0	80	10.0	80	6.7

Abbreviations: P=participant ID number, STG=superior temporal gyrus, IFG=inferior frontal gyrus

B.1. Trained items

For almost one-third of the participants (P1, P2, P6, P12, P13), the therapy set had to be complemented with items from an extra set to ensure that the therapy set included 10 items in each session. For four participants (P1, P7, P9, P11) the improvement in the l-IFG condition was larger than in the other conditions. Two participants showed the same improvement in the l-IFG and l-STG condition (P8, P13) and this improvement was larger than in the sham condition. For seven participants, because no relevant differences were found between the conditions, no optimal configuration could be determined.

B.2. Untrained items

Three participants showed lower performance after treatment; specifically, P3 in the l-IFG and l-STG condition, P7 in the l-STG condition, and P10 in the sham condition. For the remaining 10 participants, no relevant differences were found in improvement between conditions.

C. Comparing the configurations: group analyses

C.1. Trained items

Overall, post-treatment performance on trained items ranged from 0-100% correct responses, with a median of 50% (IQR: 20-85). Figure 2A shows the median and interquartile ranges (IQR) for each condition, with 50% (IQR: 20-80) correct in the sham condition, 70% (IQR: 30-95) correct in the l-IFG condition, and 50% (IQR: 20-82.5) correct in the l-STG condition. GEE analysis revealed an effect of condition, such that the post-treatment score in the l-IFG condition was significantly higher than that in the other two conditions (p=0.040). There was no effect of measurement time (p=0.943) and configuration order (p=0.669).

C.2. Untrained items

Overall, the delta scores for the untrained items ranged from -23.3-13.3%, with a median of 0% correct responses, reflecting no improvement (IQR: -3.4-3.3). Figure 2B shows the median and IQR for each condition, with 3.3% (IQR: 0-6.7) correct in the sham condition, 0% correct in the l-IFG condition (IQR: -4.95-1.65), and 0% correct in the l-STG condition (IQR: -6.7-0). GEE analysis revealed no significant effect of condition (p=0.820), measurement time (p=0.404), and configuration order (p=0.382). Pairwise comparisons revealed that the delta scores in session 1 and session 3 were significantly different (p=0.044), with a larger delta score in the first session.

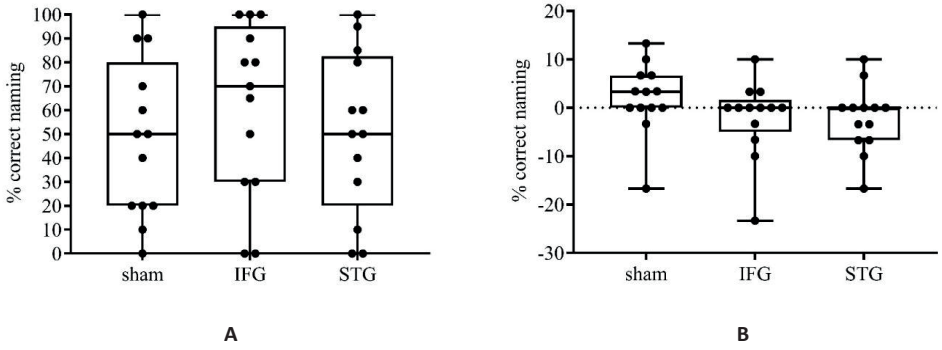

Figure 2. Results of the proportion correctly named items for the sham condition, the IFG condition and the STG condition (IFG= inferior frontal gyrus, STG= superior temporal gyrus). Figure 2a presents the results for the post-treatment results for the trained items and figure 2b presents the delta scores for the untrained items.

DISCUSSION

The aim of the present study was to evaluate a tDCS protocol, comparing different configurations within individuals and using behavioral language measures to guide optimal

electrode placement. This is the first study to include both trained and untrained picture items as outcome measures in a protocol aimed to determine an optimal configuration in a single session.

At the group level, there was a better post-treatment performance on trained items in the l-IFG condition compared to the other conditions. In line with our expectations, there was considerable variability in the individual response patterns. Almost half of the group responded more to the l-IFG condition or both active conditions; the other half showed equal performance across conditions, therefore it was not possible to determine an optimal configuration for these participants. In contrast to the trained items, there was no improvement on untrained items, indicating that one word-finding therapy session did not generalize to naming untrained items. Individual response patterns showed variable results and there were no conditions in which the improvement was relevantly larger than in the other conditions. Instead, three participants showed a lower performance after treatment. Therefore, interestingly, our protocol to determine an optimal configuration had a differential effect for trained and untrained items. However, performance on trained items may have been more suitable to detect improvements in the present study, as the trained items constituted an individualized set of material, tailored to the individual's performance level.

The group results of the trained items revealing enhanced performance in the l-IFG condition are in line with other studies showing an effect of anodal tDCS over the l-IFG.[5, 6, 18] Moreover, Marangolo et al.[5] reported an advantage of anodal tDCS over the l-IFG, compared to anodal tDCS over the l-STG and sham. However, their design differed from that of the present study in both type and duration of treatment: i.e. Marangolo et al.[5] combined tDCS with a 10-day conversational therapy treatment aiming to improve spontaneous speech in multiple sessions, whereas the present study aimed to determine an optimal electrode configuration in single sessions before starting with multiple tDCS sessions.

The lack of generalization to untrained material is in contrast with the results of Shah-Basak et al.[24]. These authors compared the effect of different electrode configurations within participants in single therapy sessions. Improvement of untrained naming performance on an 80-item picture naming task was used as an outcome measure. The authors found significant improvement on untrained items and concluded that these results could be used to determine an optimal electrode configuration for each patient. In the present study, we did not replicate such generalization to untrained items. In general, it can be assumed that there is less improvement on untrained items compared to trained items[2, 39] and generalization to untrained items may be difficult to achieve

after a single therapy session. For example, although Meinzer et al.[39] found no significant differences in performance on untrained items immediately after one treatment session, significant effects emerged during the follow-up assessments, after multiple sessions.

The differences in results between the study of Shah-Basak et al.[24] and the present study, may be related to the differences in aphasia severity between the study samples. For example, the study sample of Shah-Basak et al.[24] may have had less severe aphasia and would, therefore, respond better to treatment. Another possible explanation is that our naming task contained 30 items, whereas that of Shah-Basak et al.[24] contained 80 items; a larger set of items will be more sensitive to improvement. It was interesting to note in our study that, for some participants, both the pre scores and the post scores improved over time and the delta scores decreased across sessions, suggesting that over time there was less room for improvement. Some participants had high baseline scores in the first session, for both trained and untrained items, implying less room for improvement.

Individual analysis of the trained items revealed that six participants showed a relevantly larger improvement in the active conditions compared to the sham condition. Two of these participants, both with fluent aphasia, showed the same improvement in the l-IFG and l-STG condition; therefore, based on our protocol, it would not matter what configuration is used. For four participants, the electrode configuration did play a role, such that these participants had a relevantly larger score in the l-IFG condition; interestingly, three of these latter patients were diagnosed with non-fluent aphasia. In the study of Baker et al.[2] four of 12 patients responded to anodal tDCS over the frontal cortex. These patients had apraxia of speech and/or non-fluent aphasia, both of which are associated with left frontal damage. Therefore, the authors hypothesized that frontal stimulation may be beneficial for people with frontal damage (non-fluent aphasia).[2] Our findings support this idea since we observed that three patients with non-fluent aphasia performed better on the trained items during the l-IFG configuration. However, our study does not support the idea that people with fluent aphasia respond more to posterior stimulation, at least not in a single session. For seven participants, there were no relevant differences across conditions; for these individuals, our protocol did not provide a basis for choosing an optimal electrode configuration. The same applies to the study group of Shah-Basak et al.[24] in which five of 12 patients did not respond better to any specific configuration.

The present study has some limitations. First, no information on lesions was available for our participants, whereas lesion size/site are considered important factors in aphasia recovery and (probably) also important in determining an optimal configuration. Another limitation is the small sample size. Further, some participants reported that they found the sessions to be rather intensive. As the naming task to measure improvement on the

untrained items was always assessed at the end of each session, we cannot exclude the possibility that participants became tired/less attentive at the end of the sessions and across the sessions. Therefore, we recommend that studies using within-subject designs to study the effect of tDCS take into account the factor of time and other possible effects, such as fatigue and/or attention.

In conclusion, our protocol to determine an optimal configuration showed a differential effect for trained and untrained items, such that we could only use performance on trained items as a guidance for choosing a configuration. For some participants, it was possible to determine an optimal configuration after comparing single therapy sessions. It would be interesting to verify our protocol in future samples to elucidate which patient profiles allow to determine an optimal configuration after a single session, and also to check the effectiveness of the selected configuration in multiple therapy sessions.

SUPPLEMENTARY MATERIAL

Supplement 1. Pre and post scores for the trained and untrained items, per session.

	Trained session 1		Trained session 2		Trained session 3		Untrained session 1		Untrained session 2		Untrained session 3	
	Pre*	Post	Pre*	Post	Pre*	Post	Pre	Post	Pre	Post	Pre	Post
P1	22	5	18	6	22	9	14	18	26	26	22	20
P2	21	9	23	10	26	10	24	26	26	27	29	29
P3	15	6	14	6,5	7	6	11	11	15	8	18	15
P4	1	0	0	0	0	0	0	0	0	0	0	0
P5	4	2	1	0	2	1	0	0	1	1	3	3
P6	16	9	25	9,5	25	8	22	23	25	28	26	26
P7	9	7	20	10	11	5	9	9	13	13	18	13
P8	14	2	16	5	15	5	7	6	17	15	16	16
P9	4	5	9	4	19	7	0	2	14	13	11	12
P10	14	2	13	3	12	3	14	9	12	11	14	14
P11	3	1	2	3	2	0	1	2	3	3	5	3
P12	21	10	21	8,5	19	10	20	21	26	25	22	19
P13	20	4	21	8	21	8	16	19	19	22	18	20

* Note that the maximum pre score for the trained items is 30 and that the maximum post score is based on 10 trained items.

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CHAPTER 5

Cerebellar Cathodal Transcranial Direct Current Stimulation and Performance on a Verb Generation Task: A Replication Study.

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ABSTRACT

The role of the cerebellum in cognitive processing is increasingly recognized, but still poorly understood. A recent study in this field applied cerebellar Transcranial Direct Current Stimulation (c-tDCS) to the right cerebellum to investigate the role of prefrontal-cerebellar loops in language aspects of cognition. Results showed that the improvement in participants' verbal response times on a verb generation task was facilitated immediately after cathodal c-tDCS, compared to anodal or sham c-tDCS. The primary aim of the present study is to replicate these findings and additionally to investigate possible longer term effects. A cross-over within-subject design was used, comparing cathodal and sham c-tDCS. The experiment consisted of two visits with an interval of one week. Our results show no direct contribution of cathodal c-tDCS over the cerebellum to language task performance. However, one week later, the group receiving cathodal c-tDCS in the first visit show less improvement and increased variability in their verbal response times during the second visit, compared to the group receiving sham c-tDCS in the first visit. These findings suggest a potential negative effect of c-tDCS and warrant further investigation into long term effects of c-tDCS before undertaking clinical studies with post-stroke patients with aphasia.

INTRODUCTION

Transcranial Direct Current Stimulation (tDCS) has become increasingly popular in neuroscience and neurorehabilitation. This user-friendly noninvasive form of brain stimulation can either increase or reduce neuronal excitability in a polarity-specific manner.[1, 2] Positive or anodal stimulation is proposed to increase activity in the brain area under the electrode whereas negative or cathodal stimulation would do the opposite. tDCS has been used for fundamental research to understand the functional organization of the brain and additionally it has been investigated in a clinical setting. Examples of such clinical studies include attempts to treat patients with post-stroke aphasia or hemiplegia, Parkinson's disease, and depression.[3-6] However, despite a large body of tDCS literature reporting positive results, the reproducibility of these results is questioned.[7, 8]

Recent studies have applied tDCS to understand the different functional domains of the cerebellum, a brain structure traditionally thought to be solely related to motor control but recently suggested to also be engaged in cognitive processes.[9] A role of the cerebellum in cognitive processing is supported by reports of cognitive deficits following injury to the cerebellum as well as anatomical and neuroimaging studies.[10, 11] Topographically, cerebellar lobules VI and VII were found to have projections to cortical association areas involved in cognitive processes.[11] Neuroimaging studies have shown that regions of lobule VII are involved in prefrontal-cerebellar loops.[12-14] Specifically, language processing and executive functioning activated regions of lobule VII.[14] Taken together, these studies demonstrate the role of prefrontal-cerebellar loops in cognitive processing, specifically it has been suggested that the Purkinje cells in the right cerebellum have an inhibitory effect on the contralateral cortical prefrontal regions (i.e. cerebello-cortical inhibition).[9, 11-14]

The efficacy of cerebellar tDCS (c-tDCS) in modulating cerebello-cortical inhibition has previously been confirmed by Galea et al.[15]. They combined Transcranial Magnetic Stimulation (TMS) with c-tDCS and demonstrated that anodal c-tDCS to the right cerebellum increases the inhibitory effect to the primary motor cortex whilst cathodal c-tDCS to the right cerebellum reduces this effect. As Purkinje cells are the sole inhibitory output of the cerebellum, this observation suggests that anodal c-tDCS leads to increased activity of these neurons whilst cathodal c-tDCS leads to decreased activity. In addition, electrophysiological animal studies confirmed modulation of Purkinje cell activity with electrical stimulation.[16, 17] However, in humans, whether these changes in Purkinje cells firing are direct or depend on other cerebellar neurons is currently unknown. Given the highly homogenous anatomy of the cerebellar cortex it would seem likely that c-tDCS affects the prefrontal cortex similarly to the motor cortex. This means anodal c-tDCS would decrease prefrontal cortex activity whereas cathodal c-tDCS would increase

prefrontal cortex activity. However, literature regarding the efficacy of c-tDCS is inconsistent, for example, a study by Doeltgen et al.[18] report that anodal c-tDCS may reduce the inhibitory effect on the primary motor cortex. Also, a study focusing on language functioning[19] found that both anodal and cathodal c-tDCS enhanced the performance on a phonemic fluency task.

An interesting recent study that investigated right cerebellar involvement in cognitive processing employed c-tDCS to study prefrontal-cerebellar loops in arithmetic and language aspects of working memory and attention.[20] Pope and Miall[20] hypothesized that cathodal c-tDCS over the right cerebellum lobule VII would reduce the inhibitory tone exerted by the Purkinje cells over prefrontal regions, causing disinhibition of the contralateral prefrontal regions. Disinhibition of prefrontal regions in turn could improve performance, especially on cognitively demanding tasks. Pope and Miall used arithmetic and language tasks with varying levels of cognitive demand and, reported that the improvement in participants' verbal response times was facilitated by cathodal c-tDCS over the right cerebellum, compared to anodal or sham c-tDCS over the same region. Additionally, response times became less variable. As the improvement was greatest for the more cognitively demanding versions of the arithmetic and language task, the authors speculated that the cerebellum is capable of releasing cognitive resources by disinhibition of prefrontal regions, enhancing performance when tasks become cognitively demanding. Further support for this hypothesis was later found by demonstrating that stimulation of the prefrontal cortex with anodal tDCS achieves the same effect as cathodal c-tDCS, specifically for the task assessing arithmetic aspects.[21]

In the present study, we were specifically interested in the potential improvement in language task performance after c-tDCS, as reported by Pope and Miall.[20] Right cerebellar involvement in language processing has been highlighted in several studies.[22-24] Further, a Positron Emission Tomographic (PET) study[25, 26] and a Functional Magnetic Resonance Imaging (fMRI) study[27] have demonstrated an involvement of left hemisphere areas and the right cerebellum during a verb generation task. The application of c-tDCS may contribute to our understanding of the prefrontal-cerebellar loops and language processing in healthy subjects, but could also be interesting for future clinical applications.[28] Recent clinical studies applying cerebral tDCS in post-stroke aphasia patients have already shown promising effects[29-31] and c-tDCS might possibly further contribute to the recovery of these patients. However, the results of cerebellar stimulation on language in healthy subjects awaits replication before translation to the clinical setting is justified.

The primary aim of the present study was to replicate the facilitatory effect immediately after cathodal c-tDCS on language task performance, as reported by Pope and Miall (i.e.

their experiment 2).[20] The task setup and outcome measures are similar to their study. In contrast to their between-subject design, the present study performed a cross-over within-subject design, comparing cathodal and sham c-tDCS, in order to reduce the impact of individual variability in the response to tDCS.[32] The experiment consisted of two visits with an interval of one week; therefore, this design allowed us to investigate the long term effects of stimulation by measuring the same participants one week later.

METHODS

Design

The present study used the same task described in experiment 2 of the study of Pope and Miall.[20] Their study had a double-blind between-subject design comparing anodal c-tDCS, cathodal c-tDCS and sham c-tDCS (for further details see[20]). The present study has a double-blind cross-over within-subject design, comparing cathodal c-tDCS and sham c-tDCS (see Figure 1). The experiment consisted of two visits with an interval of one week. In each visit a different stimulation condition (cathodal or sham c-tDCS) was applied and this order was counterbalanced among participants. Similar to the study of Pope and Miall, response accuracy and verbal response times were collected before and after cathodal c-tDCS and sham c-tDCS on three language tasks: noun reading, verb reading and verb generation.

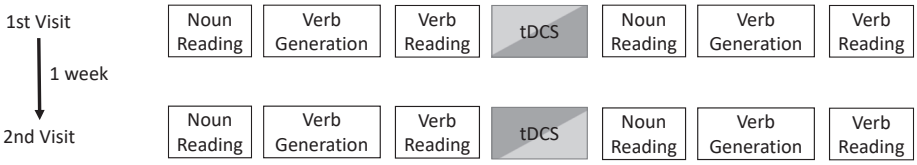

Figure 1. Study design: participants complete 2 visits with a one-week interval, receiving cathodal (dark grey) or sham c-tDCS (light grey) in a counterbalanced order.

Sample size calculation

Power calculations were based on the reported effects of the study of Pope and Miall,[20] specifically the interaction effect for verbal response times (Group x Block x Task, $F(20,570)=1.83$ corresponding to a Cohen's f of 0.18) and the interaction effect for a computed variable Learning (Session x Task x Group, $F(1,114)=4.50$ corresponding to a Cohen's f of 0.28). For a study design with 4 repeated measurements (cathodal compared to sham; before tDCS compared to after tDCS), a within-patient correlation of 0.75, an alpha of 0.05, a power of 0.80 and a Cohen's f effect size of 0.18, we need 23 subjects. For a study design with 4 repeated measurements (cathodal compared to sham; before tDCS compared to after tDCS), a within-patient correlation of 0.75, an alpha of 0.05, a

power of 0.80 and a Cohen's f effect size of 0.28, we need 11 subjects. Based on these power calculations, our aim was to include 24 subjects (in order to have an even number of subjects for the counterbalancing procedure).

Participants

Twenty-four healthy and native Dutch speakers (18 women, 6 men; age range 19-29 years, mean ± SD: 22 ± 2.36 years) with normal vision and normal speech (i.e. no stammer) were recruited from the Erasmus University Rotterdam for a small monetary reward. Exclusion criteria were left handedness and dyslexia. Right-handedness was based on an Edinburgh Handedness Inventory score ≥ 50,[33] and the absence of dyslexia was self-reported. All participants gave informed consent and the study has been approved by the Medical Ethics Committee of the Erasmus MC, University Medical Center Rotterdam.

Tasks and Stimuli

We used the three language tasks that were used in the study of Pope and Miall[20]: a noun reading task, a verb generation task and a verb reading task. For the reading tasks, participants have to read the presented noun or verb aloud as soon as it appeared on the computer screen. For the verb generation task, participants have to produce an appropriate verb as quickly as possible in response to the noun presented on the screen. For a Dutch version of these tasks, we prepared Dutch word lists including 40 nouns and 40 matched verbs. First, all nouns of the verb generation task used by Pope and Miall[20] were translated. Some of the nouns could not be translated into Dutch and some verb productions were strongly related to the morphological form of the item due to an identical word stem (e.g. *fiets- fietsen*, meaning 'bike- biking'). The list of nouns was therefore supplemented by the set of Dutch nouns of De Witte et al.,[34] resulting in a list of 124 concrete nouns related to manipulable tools and objects that were potential stimuli for the language experiment. The stimuli of the final word list were chosen on the basis of responses in a verb generation task from a pilot group ($n = 22$). Only noun-verb pairs generated by more than half of the pilot group were selected for the final word list. If two or more nouns elicited the same verb, these nouns were excluded. Also nouns eliciting non-action verbs (e.g. 'oven-bake') were excluded. The final word list, including 40 nouns and 40 matched verbs, was split up in two lists (list A and list B): one list was presented before c-tDCS and the other after c-tDCS. The order of list A and B was counterbalanced across participants. Specifically, during the first visit, half of the group was presented with list A before c-tDCS and list B after c-tDCS. During the second visit, this same group was presented with list B before c-tDCS and list A after c-tDCS. For the other half of the group the order of presentation was reversed, starting during the first visit with list B before c-tDCS, etc..

The stimuli were presented on a computer screen (48 cm x 28 cm) placed 65 cm in front of the participants. The tasks were designed and presented using MATLAB 2013a and Psychophysics Toolbox (v3.0.12).[35, 36] Each task comprised 6 blocks of 10 trials (i.e. 10 words) each. In the first five blocks the same set of words was used but the order of the appearance of the words was randomized on a block by block basis. In the sixth block a new set of words was presented, again in a randomized order. Each task lasted approximately 5 minutes. Participants had a break of at least 10 seconds between each task.

A microphone (model: Trust-MC 1200) was used to register the verbal response times. Each stimulus was replaced by the next stimulus when the microphone recorded a response. After a response was recorded, a black screen was displayed for 2 s before the next stimulus was presented.

Transcranial Direct Current Stimulation

Cathodal and sham c-tDCS were delivered through a pair of saline-soaked sponge electrodes (25 cm^2 surface area) using a NeuroConn DC-stimulator. In the cathodal stimulation condition participants received active stimulation of 2 mA for a duration of 20 minutes. Stimulation was automatically activated with a fade in of 30 s and after 20 minutes the stimulation was automatically deactivated with a fade out of 30 s. In the sham condition, participants received pseudo-stimulation with a fade in of 30 s and after 40 s the stimulation was automatically deactivated with a fade out of 30 s. The average impedance was 23.7 ± 8.0 kΩ (mean ± SD) among participants. The cathode was placed over the right cerebellar cortex, 1 cm under and 4 cm lateral to the inion, which is defined as the location of the cerebellar lobule VII. The anode was placed over the right shoulder, i.e. the right deltoid muscle.[20]

Procedure

The experiment was performed inside a quiet cubicle. Participants performed the three tasks in the following order: noun reading, verb generation and verb reading. For the reading tasks, participants were instructed to read the presented noun or verb aloud as soon as it appeared on the computer screen. For the verb generation task, they were instructed to produce an appropriate verb as quickly as possible in response to the noun presented on the screen. It was explained that an appropriate verb could be a verb that described what the presented noun may do or what it may be used for. It was emphasized that only one verb was to be produced. At the beginning of each task, one example was given and three test items were presented, which were items other than those in the experiment. For all tasks, responses were checked for accuracy by the researcher. All verbs produced during the verb generation task were written down by the researcher.

After completion of the three tasks, 20 minutes of cathodal or sham c-tDCS was applied. The electrodes were placed by the researcher. Both the researcher and the participant were blinded for stimulation condition, which was achieved by using two 5-number codes that can be entered into the tDCS device. These 5-number codes are provided by the manufacturer of the tDCS device. One code is related to start the real tDCS stimulation condition and the other code is related to start sham tDCS. A researcher of our research team (JG), who was not involved in the assessment of the experiment, provided these two 5-number codes. During the 20 minutes cathodal or sham c-tDCS, participants were instructed to look at a black computer screen. After the stimulation, participants performed the three tasks for the second time using parallel versions of word lists. In total, the experiment lasted approximately 90 minutes. After one week each participant took the experiment for the second time, in which the other stimulation condition was applied. Next to that, the word list previously presented after c-tDCS was now presented prior to c-tDCS.

Statistical analysis

Incorrect responses, missed responses, and outliers were removed before analysis. For the noun reading and the verb reading tasks, no incorrect responses were detected. For the verb generation task, non-words, multiple word responses and responses that were not representative for what the noun may do or what it may be used for (e.g. 'eyebrow – drawing'), were considered incorrect and were not included in the analysis. For each task, voice onset times were corrected manually from digital recordings if lip movement, swallowing and heavy breathing were prior to the verbal response, because this influenced the microphone recording. Outliers, responses exceeding more or less than 2 standard deviations from the mean of that task were removed. Specifically, the mean and standard deviation of all subjects' responses per task determined the outlier levels.

Although we used test items, a novelty effect was found for the first trials (i.e. first word presented) of each block, shown by a larger reaction time. Because the mean for each block consisting of 10 trials was calculated, we decided to exclude the first trial in order to get a representative mean of the data. Further, in case of violations of sphericity, a Greenhouse-Geisser correction was applied and adjusted degrees of freedom are reported in the text.

In line with the study of Pope and Miall, the present study analyzed the data in terms of the mean and variability of verbal response times. Mean verbal response times for each block per task were analyzed with a repeated measures analysis of variance (ANOVA), using four factors. These factors are Condition (cathodal tDCS and sham), Session (pre-

tDCS and post-tDCS), Task (noun reading, verb generation and verb reading) and Block (six blocks per task). The variability of verbal response times between the three tasks and six blocks per task was analyzed with pairwise comparisons; a Bonferroni correction was used. The level of significance was set at $\alpha = 0.05$. For the response variability, an ANOVA was performed on the within block standard deviations of the verbal response times across Block, Task, Session and averaged by Condition.

Also in line with the study of Pope and Miall, the present study analyzed the data by computing the variables 'learning' and 'total learning variability'. The learning variable was computed by subtracting Block 5 from Block 1 and putting this as a variable in an ANOVA with Task x Session x Condition. For the total learning variability, the standard deviations of the learning variable (Block 5 – Block 1) across Task, Session and averaged by Condition, were entered into an ANOVA.

The present within-subject design allows us to investigate the long term effects of stimulation by measuring the same subjects a week later. We therefore also performed an ANOVA including the between-subject factor visit-order. This between-subject factor indicates whether a participant received cathodal c-tDCS or sham c-tDCS at the first visit.

RESULTS

In general, results are reported in the same way as in the study of Pope and Miall.[20] Table 1 presents an overview of the statistical results for the 4 variables that were analyzed: mean verbal response times, verbal response variability, learning and total learning variability. Table 1 only includes the factors and interactions that were reported as (near) significant in the study of Pope and Miall, and will be explained further in the following paragraphs. Values are reported as mean ± standard error of the mean in the text unless otherwise specified.

Response accuracy and outliers

Participants made very few incorrect responses (1.9%) and very few missed responses (0.5%) were obtained. With regards to outliers, 3.5% of the responses were classified as outliers. The incorrect and missed responses, and the outliers were excluded from further analysis.

Verbal response times

Figure 2 presents the results of the verbal response times for each task and across the 6 blocks, before and after tDCS. In general, the range of verbal response times of the present study (0.573 s – 1.082 s) was higher than the study of Pope and Miall.[20] A Condition

x Task x Session x Block ANOVA revealed a large main effect (see Table 1) of Condition, with larger verbal response times in the sham condition (0.730 ± 0.011 s) compared to the cathodal condition (0.709 ± 0.010 s). However, there was no main effect of Session and no interaction effect of Condition x Session, therefore indicating no overall effect of tDCS on verbal response times. In line with the study of Pope and Miall, a large main effect of Task was found, with larger verbal response times on the verb generation task (0.953 ± 0.016 s) compared to the noun reading (0.606 ± 0.007 s) and verb reading task (0.600 ± 0.008 s). Also in line with Pope and Miall, a large main effect of Block was found. This can be described as a priming effect for block 1-5, meaning that the verbal response times are reduced across block 1-5 because the same words are repeated, and a novelty effect from block 5 to block 6, meaning an increase in verbal response time because new words are presented.

Table 1. Results of the study: verbal response time, response variability, learning and learning variability.

Variable	Effect	df	F	p	η2
Verbal response time	Condition	1,23	4.81	0.039	0.173
	Task	1.16,26.71	808.98	<0.001	0.972
	Block	5,115	121.63	<0.001	0.841
	Task x Block	4.22,97.15	37.16	<0.001	0.618
	Session	1,23	0.10	0.750	0.004
	Task x Session	1.38,1.20	0.77	0.427	0.032
	Condition x Task x Block	4.33,99.63	0.77	0.558	0.032
Response variability	Session	1,23	6.49	0.018	0.220
	Task	1.19,27.37	655.93	<0.001	0.966
	Block	5,115	17.63	<0.001	0.434
	Task x Block	4.31,99.12	8.65	<0.001	0.273
	Condition x Block	5,115	0.62	0.689	0.026
	Condition x Task x Block	4.00,91.96	1.42	0.233	0.058
Learning	Task	1.20,27.52	21.76	<0.001	0.486
	Task x Session	1.22,27.96	0.47	0.537	0.020
	Task x Condition	1.18,27.11	1.48	0.240	0.060
	Session x Condition	1,23	0.36	0.555	0.015
	Session x Task x Condition	1.27,29.10	0.35	0.608	0.015
Learning variability	Session	1,23	5.45	0.029	0.192
	Task	1.09,25.0	6.66	0.014	0.225
	Condition	1,23	0.63	0.435	0.027
	Task x Session	1.24,28,44	7.09	0.009	0.236
	Task x Condition	1.17,26.84	0.34	0.600	0.014
	Session x Condition	1,23	0.70	0.411	0.030
	Session x Task x Condition	1.06,24.34	0.44	0.524	0.019

The priming effect and the novelty effect were greater for the verb generation task, as shown by a large Task x Block interaction. Specifically, the verbal response times across block 1-5 were reduced more during verb generation than during noun reading and verb reading. The increase in verbal response times from block 5 to 6, was greater for verb generation than for noun reading and verb reading.

Response variability

For the response variability, a Condition x Task x Session x Block ANOVA revealed no main effect of Condition. A large main effect of Session was found, such that the response variability was greater after tDCS (0.096 ± 0.002 s) than before (0.091 ± 0.002 s). However, there was no Condition x Session interaction, indicating no overall effect of tDCS on verbal response variability.

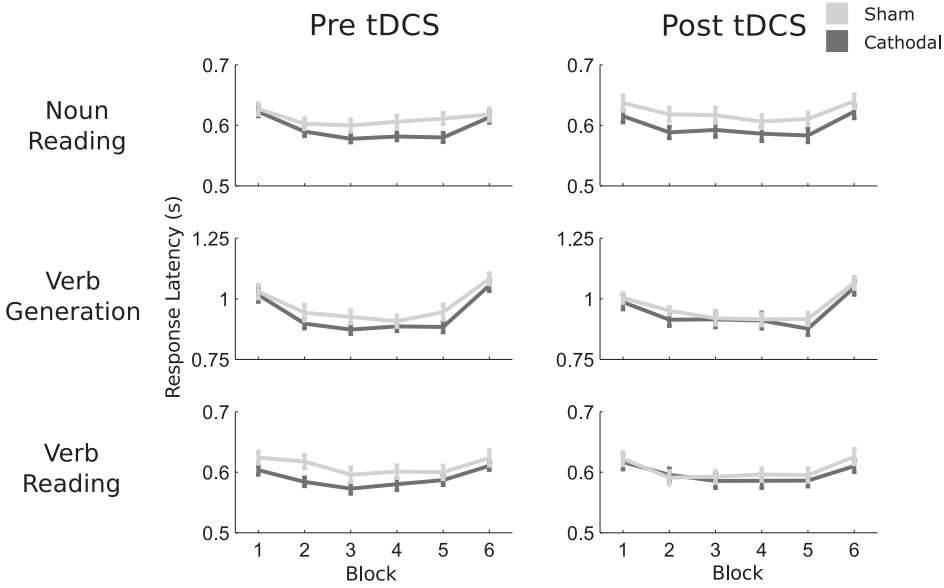

Figure 2. Results for the verbal response times (s), before and after tDCS, for each task and across the 6 blocks. Error bars present the Standard Error of the Mean (SEM).

In line with the study of Pope and Miall, there was a large main effect of Task, such that verbal response times were more variable during verb generation (0.168 ± 0.004 s) than during noun reading (0.054 ± 0.002 s) and verb reading (0.059 ± 0.002 s). Also, in line

with Pope and Miall, a large main effect of Block was found, where response variability decreased across the 5 blocks of repeated words (i.e. priming effect), then increased in block 6, when new word lists were shown (i.e. novelty effect). This pattern for the priming effect and the novelty effect was greater for the verb generation task, as shown by a large Task x Block interaction. Specifically, the response variability across block 1-5 was reduced more during verb generation compared to noun reading and verb reading. The increase in response variability from block 5 to 6 was greater for verb generation than for noun reading and verb reading.

Learning

The results for learning, as reflected in the difference in response times between block 1 and block 5, are presented in Figure 3. A Condition x Task x Session ANOVA revealed no significant main effect of Condition and no significant main effect of Session, indicating there was no effect of tDCS. In line with the study of Pope and Miall, there was a large main effect of Task, such that there was a larger improvement of verbal response times across block 1-5 for the verb generation task (0.104 ± 0.015 s), compared to noun reading (0.029 ± 0.005 s) and verb reading (0.025 ± 0.004 s). In contrast with the study of Pope and Miall, the present study did not demonstrate a Condition x Session x Task interaction.

Learning variability

For the total learning variability across block 1 to 5 (i.e. analyzing the standard deviations for the learning variable), a Condition x Task x Session ANOVA revealed no main effect of Condition. A large main effect of Session was found, such that the change in response variability was greater after tDCS (0.023 ± 0.004 s) than before (0.008 ± 0.005 s). However, there was no Condition x Session interaction, indicating no overall effect of tDCS on the change in variability. In line with the study of Pope and Miall, there was a large main effect of Task, such that the change in response variability between block 1 and 5 was greater for verb generation (0.035 ± 0.011 s), than for noun reading (0.005 ± 0.002 s) and verb reading (0.006 ± 0.002 s). A significant, large Task x Session interaction was found, such that the change in response variability between before and after tDCS was greater for the verb generation task, than for noun reading and verb reading. In contrast with the study of Pope and Miall, the present study did not demonstrate a Condition x Session x Task interaction.

Long term effects

A. Verbal response times

A Condition x Task x Session x Block ANOVA including block 1-5 and with visit-order as a between-subject factor (i.e. labeled as Visit) revealed a significant Condition x Visit

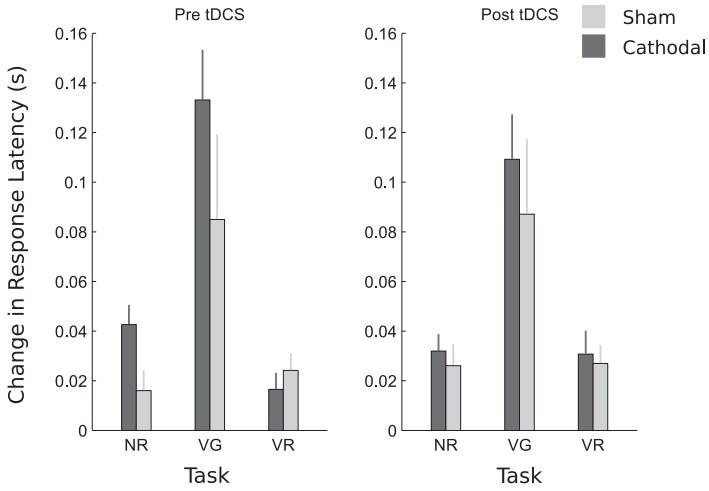

Figure 3. Results for the learning variable, calculated by subtracting the verbal response times (s) in block 5 from the verbal response times (s) in block 1. This difference is presented for each task, before and after tDCS. Error bars present the Standard Error of the Mean (SEM).

interaction, F(1,22)=8.362, p=0.008, $\eta 2$=0.275, such that the mean verbal response times showed a greater reduction for the group receiving sham in the first visit (first visit: 0.727 ± 0.016 s; second visit: 0.681 ± 0.014 s), than for the group receiving cathodal stimulation in the first visit (first visit: 0.717 ± 0.014 s; second visit: 0.715 ± 0.016 s). This effect was greater for the verb generation task, as shown by a Condition x Task x Visit interaction, F(1.294,28.470)=25.266, p<0.001, $\eta 2$=0.535. Figure 4 presents this interaction effect, showing the mean verbal response times for each task and stimulation condition, and comparing the first visit with the second visit. Specifically, the verbal response times for the verb generation task reduced more for the group receiving sham in the first visit (first visit: 0.963 ± 0.028 s; second visit: 0.864 ± 0.024 s), than for the group receiving cathodal first (first visit: 0.967 ± 0.024 s; second visit: 0.928 ± 0.028 s).

In line with the immediate c-tDCS results, the long term analysis shows a priming effect across block 1-5. Specifically, there was a Condition x Block x Visit interaction, F(4,88)=3.026, p=0.022, $\eta 2$=0.121, such that the verbal response times across block 1-5 reduced more for the group receiving sham the first time.

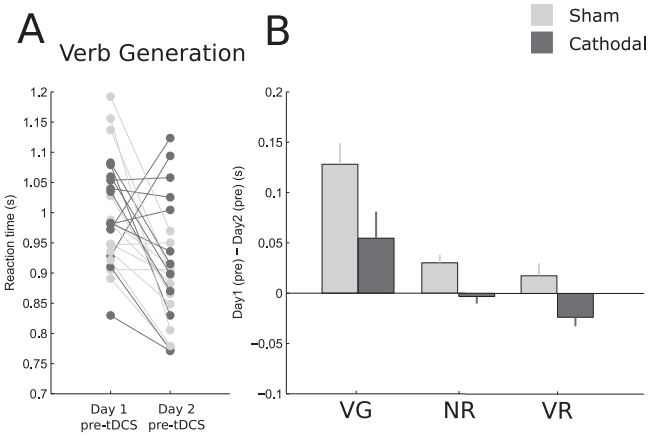

Figure 4. Results for the long term effects. Figure 4A shows the individual verbal response times on the verb generation task, for visit 1 and visit 2. Figure 4B shows the mean verbal response times for each task, subtracting performance in the second visit from the first visit. Error bars present the Standard Error of the Mean (SEM).

B. Response variability

For the response variability, the ANOVA analysis also revealed a large interaction of Condition x Visit, F(1,22)=14.274, p=0.001, $\eta 2$=0.394, such that the response variability reduced more for the group receiving sham the first time (first visit: 0.094 ± 0.004 s; second visit: 0.082 ± 0.003 s), than for the group receiving cathodal tDCS in the first visit (first visit: 0.096 ± 0.003 s; second visit: 0.089 ± 0.004 s). This effect was also more present for the verb generation task, as shown by a large, interaction effect of Stimulation x Task x Visit, F(1.558,34.280)=40.123, p<0.001, $\eta 2$=0.646. Specifically, the response variability for the verb generation task reduced more for the group receiving sham the first time (first visit: 0.171 ± 0.009 s; second visit: 0.132 ± 0.007 s), than for the group receiving cathodal the first time (first visit: 0.186 ± 0.007 s; second visit: 0.152 ± 0.009 s).

In line with the immediate c-tDCS results, the long term analysis for the response variability also shows a priming effect across block 1-5. Specifically, there was a significant interaction effect of Condition x Block x Visit, F(4,88)=2.596, p=0.042, $\eta 2$=0.106, such that the response variability across block 1-5 reduced more for the group receiving sham the first time. Finally, there was a significant interaction effect of Condition x Task x Block x Visit, F(3.728,82.018)=4.302, p=0.004, $\eta 2$=0.164, such that for the verb generation task, response variability across block 1-5 reduced more for the group receiving sham the first time.

C. Post-hoc tests: additional analysis of the long term effects

To further study the performance over time and the effect of visit-order, we have performed some additional analysis. Figure 5 presents the performance over time, for each task and across block 1-5, for the time points before tDCS visit 1 (pre-tDCS visit 1), after tDCS visit 1 (post-tDCS visit 1), before tDCS visit 2 (pre-tDCS visit 2) and after tDCS visit 2 (post-tDCS visit 2). Blue presents the group starting with the cathodal condition in the first visit and grey presents the group starting with the sham condition in the first visit.

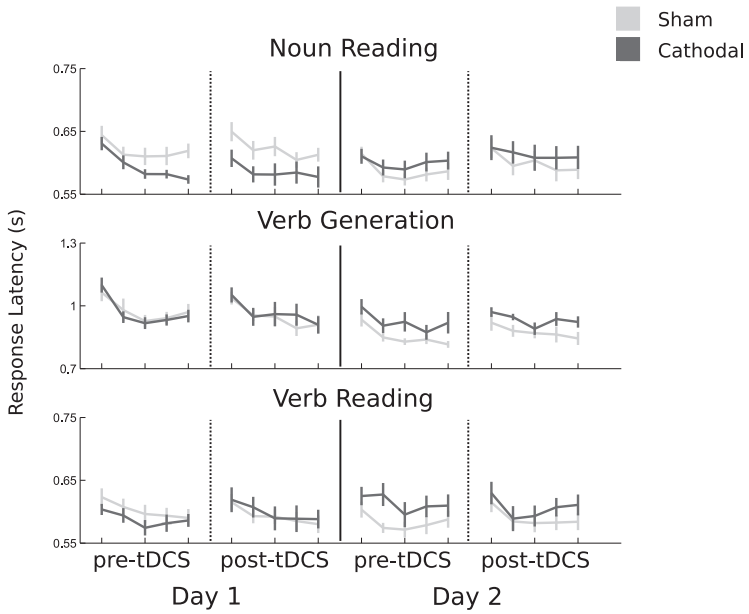

Figure 5. Verbal responses times (s) across block 1-5 and for each task, for the time points pre-tDCS visit 1, post-tDCS visit 1, pre-tDCS visit 2 and post-tDCS visit 2. Dark grey presents the group starting with the cathodal condition in the first visit and light grey presents the group starting with the sham condition in the first visit. Error bars present the Standard Error of the Mean (SEM).

We studied specifically the performance from time point post-tDCS visit 1 to the time point pre-tDCS visit 2 in order to analyze whether performance improved between visits (i.e offline learning). Also, the same set of words was under examination for these 2 time points. An ANOVA including these time points, with visit-order as the between-subject variable, revealed that the average performance across block 1-5 improves from post-tDCS visit 1 (0.719 ± 0.014 s) to the pre-tDCS visit 2 (0.693 ± 0.012 s), shown by a large effect, $F(1,22)=9.716$, $p=0.005$, $\eta 2=0.306$. This effect could be interpreted as an effect of offline learning, so participants become better in a task after a time interval. Furthermore, the group receiving sham the first time improves more for these time points (0.721 ± 0.020 s in visit 1 compared to 0.674 ± 0.016 s in visit 2) than the group receiving cathodal

tDCS the first time (0.717 ± 0.020 s in visit 1 compared to 0.712 ± 0.016 s in visit 2). This was shown by a large Stimulation x Visit interaction effect, F(1,22)=6,467, p=0.019, η2=0.227. However, these results include only the mean of all blocks, and so it is not possible to discern if any improvements in performance are a result of continued practice or if in fact performance has improved between visits (i.e. offline learning). Therefore, a further step in our analysis was to specifically analyze the time point post-tDCS block 5 of visit 1 and time point pre-tDCS block 1 of visit 2. An ANOVA including these time points, with visit-order as the between-subject variable, revealed that the performance on post-tDCS block 5 in visit 1 (0.696 ± 0.015 s) actually decreased in the pre-tDCS block 1 in visit 2 (0.730 ± 0.012 s). This was shown by a large effect of Visit, F(1,22)=9,190, p=0.006, η2=0.295. Therefore, these data show no evidence for offline learning.

DISCUSSION

The aim of the present study was to replicate the results of Pope and Miall by demonstrating that cathodal stimulation of the right cerebellum improves task performance on a verb generation task.[20] The task setup and outcome measures were similar to their study. Based on their results, showing a facilitatory effect immediately after cathodal c-tDCS, we compared cathodal c-tDCS and sham stimulation. In contrast with the between-subject design study of Pope and Miall, the present study used a cross-over within-subject design, in order to reduce the impact of individual variability.[32] Participants had to complete two visits, with half of the group receiving cathodal c-tDCS the first time and half of the group receiving sham c-tDCS the first time. Our results did not show a facilitating effect of cathodal c-tDCS on verb generation, either in terms of verbal response times or variability. In line with Pope and Miall, the verbal response times were larger for the verb generation task, compared to noun reading and verb reading. This effect can be explained with the idea that the verb generation task requires lexical search processes and verbal response selection, while noun and verb reading requires only reading processes. Interestingly, the verbal response times on our tasks were longer than those reported by the original study. These longer reaction times could be due to linguistic factors of the words,[37] for example word length, i.e. words with more phonemes need more time to process.[38] Indeed, on average, the words in our word lists were longer (mean ± SD: 6.13 ± 2.188 phonemes) than the lists of Pope and Miall (mean ± SD: 4.77 ± 1.376 phonemes).[20] Further, in line with Pope and Miall, there was a reduction in response time across block 1-5 (i.e. priming effect) and an increase in block 6 (i.e. novelty effect).

The data of the present study do not confirm that cathodal c-tDCS over the right cerebellum lobule VII leads to disinhibition of the contralateral prefrontal regions and therefore to an improved performance on a cognitive demanding task (i.e. verb generation task).

Previous studies have suggested that the Purkinje cells in the right cerebellum would have an inhibitory effect on the contralateral cortical prefrontal regions (i.e. cerebello-cortical inhibition).[9, 11-14] For language processing, right cerebellar involvement has also been suggested.[22-24] Specifically, for the verb generation task, a PET scan study and an fMRI study showed that the contralateral cerebellar hemisphere was actively involved.[25-27] However, when investigating the efficacy of c-tDCS in modulating cerebello-cortical inhibition, motor-related studies demonstrate inconsistent findings. For example, one study demonstrates that anodal tDCS to the right cerebellum increases the inhibitory effect to the primary motor cortex whilst cathodal tDCS to the right cerebellum reduces this effect.[15] In contrast, another study in this field report that anodal c-tDCS may reduce the inhibitory effect to the primary motor cortex.[18]

Furthermore, the idea that the cerebellum constraints cortical activity which can be disinhibited by cathodal c-tDCS is also not consistently supported by cognition-related tDCS studies. For example, studies show contradictive results with regards to the application of tDCS to the right cerebellum and its effects on the performance on a verbal Working Memory (WM) task, i.e. forward and backward digit span task. One study shows that cathodal c-tDCS leads to reduced forward digit span and blocks the practice dependent increase in backward digit span,[39] while another study[40] shows that both anodal and cathodal tDCS impairs practice dependent improvement in reaction times in a WM task. Further, Turkeltaub et al.[19] found that both anodal and cathodal c-tDCS enhanced the performance on a phonemic fluency task, however, the anodal effect was found to be more robust. Taken together, it seems that c-tDCS studies are not yet consistent whether anodal or cathodal c-tDCS improves or disrupts task performance in healthy subjects. Future studies need to further explore the specific polarity effects of c-tDCS in order to understand its usage for cerebellar dependent cognitive processing.

Interestingly, we observe a long term effect of c-tDCS in our data. When analyzing the data further by taking into account visit-order, we found that the group receiving cathodal c-tDCS the first time demonstrated poorer performance in the second visit in comparison to those who received sham stimulation the first time. First of all, the group receiving cathodal c-tDCS in the first visit demonstrate less improvement from visit 1 to visit 2. Also, the group receiving cathodal c-tDCS in the first visit show less improvement during the second visit (i.e. performance across block 1-5) compared to the group receiving sham the first time. Regarding response variability, the same findings are found, thus the group receiving cathodal c-tDCS in the first visit show increased variability in verbal response times in the second visit and during the second visit (i.e. increased variability across block 1-5). In motor-related studies, this long term effect is often called a consolidation effect, meaning that after acquisition performance can become resistant

to decay.[41] To our knowledge, studies investigating consolidation effects of c-tDCS on a language task are scarce, whereas there are several motor-related c-tDCS studies that investigate the effect of c-tDCS on a longer time scale. For example, one such study demonstrated that anodal c-tDCS would enhance general motor skill learning and sequence-specific learning, 35 minutes after tDCS stimulation.[42] Another study shows that anodal c-tDCS to the right cerebellum improves task performance on a temporal motor task in the follow-up tests (90 minutes and 24h after training).[43] Furthermore, a recent study provides evidence that cathodal c-tDCS impairs overnight retention of a force field reaching task.[44] Therefore, these motor-related studies show that, on a longer time scale, anodal c-tDCS may enhance performance, while cathodal c-tDCS may impair performance, which is in line with the long term results of the present study.

Studies focusing on the adaptation of movements and tDCS have demonstrated a dissociation between the acquisition phase and the consolidation phase.[45, 46] Specifically, anodal tDCS to the right cerebellum leads to an increased acquisition of new internal models whereas anodal tDCS to the motor cortex leads to improved consolidation. Therefore, the cerebellum is believed to rapidly acquire new internal models that are also quickly forgotten whereas the motor cortex learns more slowly but retains better (i.e. consolidation). A similar transfer of learning from the cerebellar cortex to other structures has been proposed for other cerebellar dependent adaptation tasks such as eye-blink conditioning or adaptation of the vestibule-ocular reflex.[47] In the present study, it is possible that these two partially separable effects are at work: short terms changes in firing rate of the cerebellum and additional effects on plasticity. First, cathodal c-tDCS may indeed reduce the firing rate of Purkinje cells and the inhibitory tone on the prefrontal cortex, and therefore improve performance in tasks relying on these cortical areas, as found in the study of Pope and Miall. However, it should be noted that there is no direct neurophysiological evidence for this effect of c-tDCS specifically on the prefrontal cortex. Secondly, cathodal c-tDCS may also reduce plasticity in the cerebellar cortex and therefore retard the rate of learning there, subsequently reducing the amount that can be transferred to other areas for consolidation, which may be in line with the results of the present study.

The present within-subject design with several time points allows us to evaluate different sub-concepts of consolidation. Consolidation can be described in terms of offline learning, i.e. improvements in performance between visits, and memory stabilization, i.e. reduced performance compared to the end of the previous visit but increased performance in comparison to the naïve state.[48] However, the degree to which either or both of these is possible is dependent on task structure and the particular skill under consideration. An important consideration in interpreting our results is separating the

effect of repeated practice from true offline learning. The results of the present study show that the average performance across block 1-5 improves from time point post-tDCS in the first visit to time point pre-tDCS in the second visit. Furthermore, the group receiving sham the first time improves more for these time points than the group receiving cathodal stimulation the first time. Therefore these results may show an effect of offline learning, however, if only the mean of all blocks is used as a measure of performance it is not possible to discern if any improvements are a result of continued practice or if in fact performance has improved between visits.[48] Further analysis demonstrates that performance in both groups (i.e. the group receiving cathodal stimulation the first time and the group receiving sham the first time) decreased between block 5 of the first visit and block 1 of the next, despite the fact that the same set of words was under examination. These data therefore show no evidence for offline learning but that may be due to the relatively long period of time between visits or because this particular task is not appropriate for such changes. In the future it will be interesting to test subjects again after a shorter interval to assay if offline learning is indeed possible with this task. It is important to note that offline learning has been investigated in an fMRI learning paradigm in which subjects had to learn a new lexicon and were tested 20 minutes later.[49] The degree of offline learning was positively correlated with the level of activation of the right cerebellum. Therefore, these data provide evidence for a role of the cerebellum in consolidation of a learning task that includes language/linguistic aspects. The differences between learning a new lexicon and learning associations within a known lexicon (as here), especially when concerning the cerebellum, are unknown and it is vital for proper delineation of tDCS effects that the specific task demands are well understood.

Limitations of the study

First of all, it should be noted that the design of the present study with 1 week between 2 visits could interfere with replication of the original immediate effect reported by Pope and Miall. This interference could be due to effects of retesting the same words or a ceiling effect. Furthermore, in the present study the subjects had one block of novel words at the end of the five blocks of repeated words which may have also acted as an interfering factor. As the majority of the results found in both the present study and the original Pope and Miall study can be found within blocks 1-5 it would be interesting to repeat the experiment with the omission of the novel words in block 6 to test if any interference is occurring. Finally, it should be noted that the majority of (c-)tDCS studies are described in the context of motor tasks and we therefore used these studies in order to interpret our results, however, the analogy between motor learning, consolidation and the type of results presented here may be stretched.

Conclusion and future recommendations

The present study shows that long term effects of c-tDCS need to be taken into account when investigating the effect of c-tDCS on language task performance. Most tDCS studies with a motor or non-motor learning task focus on direct results rather than long term learning effects (i.e. consolidation). Our findings warrant further investigation into long term effects of c-tDCS, to better capture its effect and how we can use this application to understand the complex role of the cerebellum on cognitive/language processing. Therefore, we first need to understand c-tDCS in healthy subjects, before undertaking clinical studies with post-stroke patients with aphasia. To further explore the long term effect of c-tDCS on a cognitive language task, we would suggest to combine the design of Pope and Miall with the design of the present study. This combined design would describe the effect of c-tDCS in 3 conditions - anodal c-tDCS, cathodal c-tDCS and sham (between-subject) - and participants need to come twice in each condition (within-subject). This design allows us to evaluate the effect of anodal c-tDCS compared to the effect of cathodal c-tDCS, on a longer time scale. Furthermore, techniques such as EEG may be used to explore the effect of cerebellar tDCS and its polarity specific effects on ongoing or induced activity in areas of the cortex associated with language.

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CHAPTER 6

The Role of the BDNF Val66Met Polymorphism in Recovery of Aphasia After Stroke.

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ABSTRACT

Background Brain-derived neurotrophic factor (BDNF) is assumed to play a role in mediating neuroplasticity after stroke. Carriers of the function-limiting Val66Met (rs6265) single nucleotide polymorphism (SNP) may have a downregulation in BDNF secretion which may lead to a poorer prognosis after stroke compared to non-carriers in motor learning and motor function recovery. The present study investigates whether this polymorphism may also affect the recovery of post-stroke aphasia (i.e. language impairment).

Objective To study the influence of the BDNF Val66Met polymorphism on the recovery of post-stroke aphasia.

Methods We included 53 patients with post-stroke aphasia, all participating in an inpatient rehabilitation program with speech and language therapy. All patients were genotyped for the Val66Met SNP and subdivided into carriers (at least one Met allele) and non-carriers (no Met allele). Primary outcome measures included the improvement over rehabilitation time on the Amsterdam-Nijmegen Everyday Language Test (ANELT) and the Boston Naming Test (BNT).

Results The outcome measures showed a large variability in the improvement scores on both the ANELT and BNT. There was no significant difference between non-carriers and carriers in the primary outcome measures.

Conclusion This study investigated the effect of the BDNF Val66Met polymorphism on clinical recovery of post-stroke aphasia. In contrast to earlier studies describing a reducing effect of this polymorphism on motor function recovery after stroke, the present study does not support a reduction in language recovery for carriers compared to non-carriers with post-stroke aphasia.

INTRODUCTION

Stroke is a leading cause of adult disability. About one third of stroke patients will develop any form of aphasia, a deficit of language processing[1, 2] in one or more language modalities, i.e. speaking, writing, auditory comprehension and written comprehension.[3] Many patients show incomplete recovery and aphasia has a disruptive effect on social participation. Many report to feel isolated and experience distress due to communication impairments.[4] In the first weeks to months, people with aphasia may recover as a result of spontaneous recovery.[5] There is evidence that Speech and Language Therapy (SLT) has a beneficial effect on functional communication, with therapy intensity, dose and duration as important determinants.[3]

Recovery of language after stroke is mediated by neuroplasticity processes. Brain-derived neurotrophic factor (BDNF) is a neurotrophin that plays an important role in these processes.[6-8] BDNF levels would increase after stroke which would promote neuronal survival by e.g. attenuating glutamate toxicity[9] and therefore it plays an important role in spontaneous recovery after stroke. Further, animal studies have shown that BDNF promotes long-term potentiation (LTP) through TrkB signaling.[10-12] which is thought to be crucial for episodic memory processing in the hippocampus.[13, 14] Studies have shown a downregulation of LTP by activated BDNF-TrkB signaling in the hippocampal synapses of BDNF-knock-out mice[15-17], and poorer LTP in mice with a genetically modified gene coding for BDNF[15, 18] corresponding to reduced learning performance.[19-22] Therefore, these animal studies show that BDNF is involved in LTP processes which may underlie learning.

The BDNF Val66Met polymorphism is a gene variation, where at least one Met allele is present. In humans, 30% of the general Caucasian population are carriers of a Met allele, up to 70% in the Asian population.[23] In mice, carriers of a Met allele show a deficiency in activity-dependent release of BDNF, leading to a downregulation of LTP. In humans, this decrease in LTP in carriers was related to a reduced hippocampal volume and downregulated episodic memory storage.[14, 24, 25] Carriers of a Met allele show a smaller hippocampal volume and more deficits in motor learning and skill acquisition.[6, 14, 17, 26-28] However, whether a reduced capacity to memorize and learn language skill also translates to recovery from aphasia after stroke has not yet been investigated.

In the context of stroke recovery, some studies have shown that the Val66Met polymorphism is associated with slower or reduced (behavioral) recovery after stroke, based on general stroke outcomes or motor skill learning.[29-31] Studies on general outcomes after stroke show a large variety of populations in terms of ethnicity, age and time post-stroke.[31-34] So far, many studies on stroke survivors have focused on motor skill learning

and motor function recovery.[31, 33-38] whereas, to our knowledge, literature on the role of the BDNF polymorphism in language recovery after stroke is scarce.[36] As aphasia has a great impact on the life of stroke patients, and aphasia training requires sufficient adaptive learning skills, it would be interesting to understand the role of the BDNF Val66Met polymorphism in language recovery after stroke and its potential effect on the variability in outcome among stroke patients with aphasia.

The aim of the present study is to investigate the role of the BDNF Val66Met polymorphism in recovery of aphasia after stroke.[14] We hypothesize that carriers of at least one Met allele show a reduced improvement of language recovery compared to non-carriers. This hypothesis is based on two assumptions. First, the BDNF Val66Met polymorphism may decrease the release of BDNF and therefore might interact with spontaneous recovery processes post-stroke. Second, BDNF would promote LTP; it influences activity-dependent plasticity, and would contribute to learning processes based on behavioral experience (i.e. speech and language therapy, SLT). Therefore, the decreased BDNF release in the polymorphism may lead to less behavioral recovery following SLT. We studied the impact of the polymorphism in a group of stroke patients with aphasia, who received regular aphasia rehabilitation in the sub-acute phase after stroke, by comparing treatment outcomes between non-carriers (no Met allele) and carriers (at least one Met allele).

METHODS

Participants

From July 2014 to June 2016 stroke patients were recruited from three stroke rehabilitation centers in the Netherlands: Rijndam Rehabilitation, Libra Rehabilitation and Audiology, and Revant Rehabilitation Center. Inclusion criteria were: aphasia after stroke, enrolment in an inpatient stroke rehabilitation program including SLT, native speaker of Dutch, time post onset less than three months, age 18-80 years at the time of stroke. Exclusion criteria were: prior stroke resulting in aphasia, excessive use of alcohol or drugs, premorbid (suspected) dementia, premorbid psychiatric disease affecting communication.

The presence of aphasia was diagnosed at admission to the rehabilitation institute, where patients are first seen by a medical specialist in Physical Medicine and Rehabilitation, who refers all patients with problems in language and communication to experienced language and speech therapists (SLTs). SLTs perform a standard set of standardized Dutch aphasia tests, to diagnose the presence of aphasia. This standard set includes at least the ScreeLing,[39, 40] 72 items (cutoff score: 66), and an expert rating of the Aphasia

Severity Rating Scale (ASRS) from the Akense Aphasia Test (AAT).[41, 42] Premorbid aphasia was excluded based on medical records.

During the first week of admission to the rehabilitation center, patients were asked to consider participation in the study. All patients provided written informed consent before inclusion. The study was approved by the Medical Ethics Committee (MEC) of the Erasmus MC, University Medical Center Rotterdam.

Design

For this study, we used a prospective follow-up study design. Language functioning was routinely tested by the SLTs at admission and at discharge from the rehabilitation clinic. We compared two groups of stroke patients with aphasia based on the Val66Met polymorphism: non-carriers (genotypes with two Val alleles), and carriers (genotypes with at least one Met allele).

Intervention

As part of their inpatient stroke rehabilitation program, all patients received SLT, 2-5 hours per week. Regular SLT for inpatients includes a detailed assessment of language functioning and verbal communicative abilities at intake, prior to formulating an individually tailored therapy program, which is designed to meet individual needs and capacities. In the first weeks to months, the focus will be on cognitive-linguistic therapy, i.e. disorder-oriented therapy to optimize language processing at the affected linguistic levels (semantics, phonology, syntax). Later in the rehabilitation process, when language recovery is reaching a plateau, the focus of therapy shifts to communicative strategies.

Measures

Outcome measures were the improvement on the Amsterdam Nijmegen Everyday Language Test (ANELT) measuring communication in daily life situations[43] and on the Boston Naming Test (BNT), a picture naming task to measure word finding.[44] ANELT scores range from 10 to 50, and the BNT scores range from 0 to 60.[45] Relevant documented information of the stroke were date of onset and type of stroke (ischemic or hemorrhagic). Demographic data included: age, gender, handedness (Edinburgh Handedness Inventory), presence of a partner, and educational level (ISCED classification 2011).

Genetics

We took saliva samples (Oragene Discover OGR-500, DNA Genotek Inc., Ottawa, Ontario, Canada) from each patient to determine the presence of the BDNF Val66Met single nucleotide polymorphism (SNP). There are three variants; homozygotes with either two Val66 alleles or two Met66 alleles, and heterozygotes with both a Val66 and a Met66

allele. Patients without a Met allele were classified as non-carriers (Val group), patients with at least one Met allele as carriers (Met group).

The BDNF Val66Met SNP (rs6265) was genotyped with TaqMan Allelic Discrimination using the Assay-On-Demand service of Life Technologies. Reactions were performed in a 384-wells format in a total volume of 2 µL containing 2 ng DNA, 1x TaqMan assay, and 1x genotyping master mix (Thermo Scientific, Thermo Fisher Scientific, Waltham, Massachusetts, USA). PCR cycling consisted of initial denaturation for 15 minutes at 95°C, and 40 cycles with denaturation of 15 seconds at 96°C and annealing and extension for 60 seconds at 60.0°C. Signals were read with the TaqMan 7900HT (Life Technologies, Thermo Fisher Scientific, Waltham, Massachusetts, USA) and analyzed using the sequence detection system 2.4 software (Life Technologies, Thermo Fisher Scientific, Waltham, Massachusetts, USA).

Sample size calculation

For the sample size calculation we used routinely collected data on outcomes of regular language training in the rehabilitation clinic. Based on these data we aimed to detect a minimal difference between non-carriers and carriers of 10 points improvement on the BNT, with a standard deviation of 12, leading to an estimated effect size of 0.833. Using an alpha of 0.05, a power of 0.80, and taking into account that 30% of the patients are carrier of at least one Met allele, we estimated that a total sample size of 54 patients was required.

Data analysis

Differences in demographic characteristics between the two groups were analyzed with an independent t-test for continuous variables, a Mann-Whitney U Test for variables on an ordinal scale, and the chi-square test for categorical variables. We performed a Kolmogorov-Smirnov test to test whether the distribution of the delta scores of the ANELT and BNT was significantly different from a normal distribution. Results reveal that both the ANELT delta scores ($D(48)= 0.149$, $p=.010$) and the BNT delta scores ($D(48)= 0.137$, $p=.024$) differed significantly from a normal distribution, probably caused by a substantial number of patients without improvement (delta score = 0) on both tests.

Change over time within each group and differences between the two groups in improvement on the language tests (T0-T1), were analyzed with Generalized Estimating Equations (GEE), which takes into account that multiple measurements within patients are correlated. GEE is a semiparametric method, which does not depend largely on the specification of the underlying distribution of the outcomes. It is also flexible in handling missing data. The outcomes on the language tests at T0 and T1 were the dependent

variables in the GEE models, in which the measurement time (T0 vs T1) and group membership (carriers vs non-carriers) were entered as fixed variables. To study differences in improvement between the groups the interaction between group and time was added to the models. The effect of potential confounders was analyzed if significant differences were found between the groups at baseline. The level of significance (p) was .05 in all analyses. IBM SPSS 21 Statistics software was used for all statistical tests.

RESULTS

We included 60 patients during an inclusion period of two years (data are available upon request from the corresponding author). We were able to collect BDNF data of 53 patients, as seven patients were unable to fill up the saliva samples due to oral apraxia. For some participants scores on either T0 or T1 were missing, namely 3% of the BNT scores and 5% of the ANELT scores were missing. For baseline characteristics, see Table 1.

Table 1. Demographic baseline characteristics for non-carriers and carriers.

	All patients n=53	Non-carriers n=32 (60%)	Carriers n=21 (40%)	p-value (two-tailed)
Gender				.296
- Men	36 (68%)	20 (63%)	16 (76%)	
- Women	17 (32%)	12 (37%)	5 (24%)	
Age (years; mean, SD)	58.5 (10.6)	58.5 (11.2)	58.5 (9.6)	.979
Education				.509
- Up to secondary school (%)	26 (49%)	17 (53%)	9 (43%)	
- Up to college (%)	20 (38%)	11 (34%)	9 (43%)	
- Up to ac./post-doc (%)	7 (13%)	4 (13%)	3 (14%)	
Partner, yes (%)	33 (62%)	23 (72%)	10 (48%)	.075
Type of CVA				.922
- Ischemic (%)	40 (75%)	24 (75%)	16 (76%)	
- Hemorrhagic (%)	13 (25%)	8 (25%)	5 (24%)	
Time post-onset (days; mean, SD)	25.9 (22.7)	24.3 (19.4)	28.4 (27.1)	.361
Time T0-T1 (days; mean, SD)	58.2 (26.9)	57.4 (26.8)	59.4 (27.2)	.714

The Val group consisted of 32 patients (60%), the Met group of 21 patients (40%), including two patients with two Met alleles. At baseline, there were no significant differences between the groups. However, there was a trend for having a partner, such that non-carriers more often had a partner compared to the carriers, X^2 (1, N=53) = 3.18, p=.075. The Met group contained more men than women (76% men), although this was not

significantly different from the gender distribution in the Val group (63% men; X^2 (1, N=53) = 1.09, p=.296).

On both language tests there was a large variability in baseline scores in both groups and there was also considerable variability in improvement on both language tests, as shown in Figure 1 (ANELT) and Figure 2 (BNT).

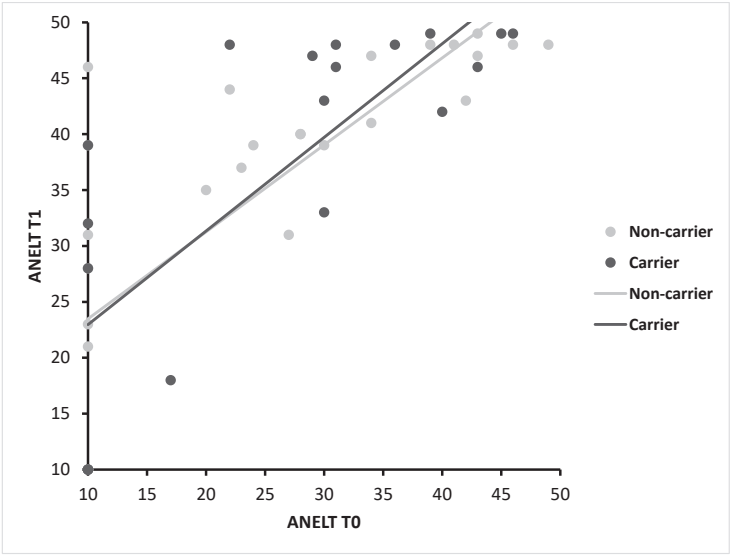

Figure 1. Individual scores on the ANELT at admission and discharge with regression lines for the Val group (light grey) and Met group (dark grey).

Within each group the improvement over time was significant for both tests (Table 2). The Val group improved significantly on the ANELT (estimated mean difference=10.15, p<.001) and on the BNT (estimated mean difference=13.39, p<.001). The Met group improved significantly on the ANELT (estimated mean difference=10.20, p<.001) and on the BNT (estimated mean difference=14.46, p<.001). Differences in improvement between the two groups were not significant, neither on the ANELT (estimated mean difference=0.05, p=.984), nor on the BNT (estimated mean difference=1.07, p=.770). Subgroup analyses for having a partner did not show any evidence for a significant difference in improvement between the Val and Met group.

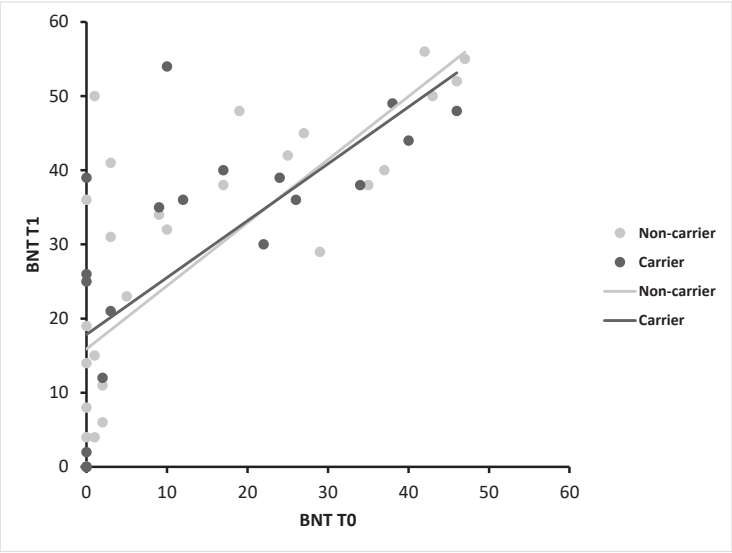

Figure 2. Individual scores on the BNT at admission and discharge with regression lines for the Val group (light grey) and Met group (dark grey).

Table 2. Estimated means, improvement scores, and mean differences in language outcomes between carriers and non-carriers.

	Non-carriers		Carriers		Mean difference*	95% CI	p-value
	Mean*	SE	Mean*	SE			
ANELT T0	25.0	2.4	27.5	2.9	2.51	-4.89 – 9.90	.506
ANELT T1	35.2	2.4	37.7	3.1	2.56	-10.31 – 5.19	.517
Improvement ANELT T0-T1	10.2	1.7	10.2	2.1	0.05	-5.21– 5.32	.984
BNT T0	15.4	3.1	14.5	3.3	-0.93	-9.79 – 7.93	.837
BNT T1	28.8	3.5	28.9	3.7	0.14	-10.10 – 9.81	.977
Improvement BNT T0-T1	13.4	2.3	14.5	2.9	1.07	-6.13 – 8.28	.770

*estimated means, based on GEE analyses

DISCUSSION

The aim of our study was to investigate the influence of the BDNF Val66Met polymorphism on language recovery in patients with post-stroke aphasia. In a prospective follow-up study, the BDNF Val66Met polymorphism was determined in a group of 53 stroke patients with aphasia, who received regular aphasia rehabilitation in the subacute phase after stroke. Thirty-two were non-carriers of a Met allele and 21 were carriers (at least one Met allele). Language recovery in each group was quantified by assessing

the ANELT and BNT at admission and discharge at the clinic. The results showed no significant differences between the carriers and non-carriers in the level of improvement on either the ANELT or BNT, in contrast to our expectations.

The results of our study are in line with one previous study,[36] although this study differed from our study in several ways. The authors focused on brain stimulation and therapy consisted of rTMS or sham stimulation together with language therapy. Further, they used other outcome measures (Aphasia Severity Rating Scale) and included only ischemic stroke patients. Despite these differences, the results also suggest that the BDNF polymorphism does not influence aphasia recovery after stroke.

In our study the Met group contained relatively more men (76%) compared to the Val group (63% men), however this difference did not reach significance. In other studies on the relation between the BDNF Val66Met polymorphism and neuroplasticity after stroke no gender differences were described. One study with stroke patients reported higher BDNF serum levels in male carriers compared to male non-carriers, but showed no meaningful gender-related differences in concentration of BDNF serum.[46] Also, the distribution of the BDNF polymorphism in healthy subjects (mainly elderly) and stroke patients did not show dissimilarities in gender.[47, 48] Taking into account these results, we assume that the high number of men in the Met carriers in our study group should be considered a coincidence.

In the present study, we included both ischemic and hemorrhagic strokes. Previous research on the BDNF polymorphism did not show any relation with the type of stroke.[49] Concerning outcome after stroke, studies have reported contradictory findings. Whereas the BDNF polymorphism did not seem related to general – unspecified – outcomes in a study in hemorrhagic stroke patients,[8] the outcomes of recovery after three months was described as poorer among those with a Met allele in Chinese ischemic stroke patients.[33] The difference in general outcome after stroke might also be explained by the plasticity of specific intra-cortical regions, which might be polymorphism specific.[8]

The results of the present study do not support our hypothesis that BDNF plays a role in the early phase of language recovery after stroke, when spontaneous recovery interacts with treatment. Studies have shown that BDNF would underlie learning processes, however the exact role of learning processes in early language rehabilitation is largely unknown. The interaction between spontaneous recovery and treatment in the early phase post-stroke remains disputable. One recent study has found no difference in language recovery between a group receiving intensive aphasia treatment compared to a

group receiving no treatment.[50] In the context of the present study, it would be interesting to investigate how BDNF may interact with SLT in the chronic phase.

Limitations

The present study has several limitations. First, there was large variation in the improvement of scores on both tests over time, decreasing the chance of detecting a significant difference in a relatively small group of participants. The duration of rehabilitation also varied between patients, depending on many factors (such as severity of stroke, conditions for discharge, social factors), which may also have influenced the progress of recovery during the inpatient rehabilitation.

Furthermore, we did not take into account the severity of stroke. Neuroplasticity might be reduced by the impact and volume of the stroke, as well as the overall intensity of the inpatient rehabilitation program. For example, increased time spent on motor training will give the patient less time to process the aphasia training skills. We did not find any studies describing the relation between lesion volume and BDNF polymorphism on language outcome after stroke.

Third, although aphasia was the most prominent symptom in our participants, a concomitant apraxia could not be excluded. In clinical practice, it is hard to disentangle the impact of apraxia of speech on language performance in people with aphasia. Therefore we cannot exclude that the presence of apraxia may have had some impact on test performance.

Conclusions

To our knowledge, this study is the first to investigate the effect of BDNF Val66Met polymorphism on neuroplasticity in aphasia after stroke. In contrast to studies describing an effect of the BDNF polymorphism on motor learning and motor function recovery, we found no significant difference in language recovery between post-stroke aphasia patients carrying a Met allele compared to non-carriers. Therefore, the present results suggest that the BDNF polymorphism does not significantly influence aphasia recovery through SLT after stroke. However, genotyping this polymorphism after stroke might still be valuable to further unravel the mechanisms that determine recovery of aphasia after stroke. Future longitudinal studies are needed to investigate the influence of the BDNF polymorphism on language recovery during stroke rehabilitation. It might be interesting to investigate whether a distinction can be made between language recovery and language learning after stroke. Multiple measurements should be performed over time within a larger study population, to study recovery patterns during the (sub)acute and chronic phase and to study the effect of covariables e.g. stroke severity or type of stroke.

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CHAPTER 7

Maladaptive Plasticity in Aphasia: Brain Activation Maps Underlying Verb Retrieval Errors.

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ABSTRACT

Anomia, or impaired word retrieval, is the most widespread symptom of aphasia, an acquired language impairment secondary to brain damage. In the last decades, functional neuroimaging techniques have enabled to study the neural basis underlying anomia and its recovery. The present study aimed to explore maladaptive plasticity in persistent verb anomia, in three male participants with chronic non-fluent aphasia. Brain activation maps associated with semantic verb paraphasia occurring within an oral picture-naming task were identified with an event-related fMRI paradigm. These maps were compared with those obtained in our previous study examining adaptive plasticity (i.e. successful verb naming) in the same participants. The results show that activation patterns related to semantic verb paraphasia and successful verb naming comprise a number of common areas, contributing both to maladaptive and adaptive neuroplasticity mechanisms. This finding suggests that the segregation of brain areas provides only a partial view of the neural basis of verb anomia and successful verb naming. Therefore, it indicates the importance of network approaches which may better capture the complexity of maladaptive and adaptive neuroplasticity mechanisms in anomia recovery.

INTRODUCTION

Anomia, or impaired word retrieval, is the most prominent and widespread symptom of aphasia, an acquired language impairment that can result from a focal brain lesion.[1] In the context of oral word retrieval, different types of errors (i.e. paraphasia) can occur, including phonemic paraphasia, semantic paraphasia, neologisms and circumlocutions (i.e. using devious ways to describe words).[2]

The present study focuses on semantic paraphasia in the context of verb retrieval. Verbs carry a critical meaning since they have important functions in the structural formulation of sentences.[3] Therefore, verb paraphasia has a considerable impact on an individual's capacity to convey meaning, which can lead to a substantial handicap. A semantic verb paraphasia occurs when a target verb is replaced by a semantically related verb,[4] such as saying 'running' instead of 'walking'. Research on the cognitive mechanisms underlying the production of semantic paraphasia shows that these may result from impaired phonological processing, or impaired semantic processing, or a combination of both.[5]

Functional neuroimaging techniques allow to study the neural basis underlying verb production and anomia, and its recovery. The neural substrate of verb production involves a left frontal cortical network, including the left prefrontal cortex,[6] the left superior parietal lobule, the left superior temporal gyrus,[7] the left superior frontal gyrus,[8] and the primary motor cortex, in the posterior portion of the precentral gyrus.[9-11] In the context of verb anomia, the production of semantic paraphasia may reflect damage of these language-related areas, as well as an attempt to compensate for the impairments resulting from this brain damage as there is a semantic relation between the target and response.[12] This attempt to compensate can be related to the concept of neuroplasticity which refers to a number of brain mechanisms involved in learning and relearning, and can be reflected by changes in brain activation patterns highlighted by functional magnetic resonance imaging (fMRI).

Two main forms of neuroplasticity have been studied: functional reactivation, which occurs when previously damaged and inactive areas recover their function after a latency period,[13] and functional reorganization, which reflects compensation of the permanent damage of specific brain areas by the recruitment of some other areas not previously involved in language processing.[12] Different types of neuroplasticity may occur during anomia recovery: if this results in functional recovery (as reflected by successful word retrieval) neuroplasticity is defined as adaptive, whereas when errors (such as paraphasia) persist neuroplasticity is considered to be maladaptive.[14, 15]

There is an ongoing debate regarding the functional reorganization in anomia recovery and whether these compensatory processes reflect adaptive or maladaptive plasticity. The left cerebral hemisphere (LH) is considered the dominant hemisphere in language processing, at least in right-handed individuals.[16] The fMRI literature has many reports in which LH damage is followed by a shift of language processing to the right cerebral hemisphere (RH), i.e. laterality shift.[17-20] However, the extent to which this RH shift reflects adaptive or maladaptive neuroplasticity remains controversial. Some studies focus on the benefits of RH recruitment[21] and emphasize the role of the RH in language processing in healthy subjects.[22] Others suggest that RH recruitment leads to persistent errors, reflecting maladaptive plasticity.[23] Compared to the LH, the RH may have broad overlapping semantic maps: in this case lexical selection processing would be less semantically specified and would be associated with semantic paraphasia.[24] Another view is that RH recruitment could be beneficial in the short term whereas, in the long term, it could contribute to an incomplete or less efficient improvement compared with a better recovery sustained by the reactivation of LH language processing areas.[18-20, 25-27] Moreover, the extent to which RH recruitment is adaptive or maladaptive may depend on lesion size.[12, 26] These latter authors argue that, while minimal damage to core language processing areas leads to maladaptive RH recruitment, extended LH lesions may trigger adaptive RH recruitment by release of the RH potential to process language. Overall, the literature presents a largely negative view on the impact of RH recruitment in the context of aphasia and anomia recovery, in particular in cases of moderate LH damage.

One way of examining the extent of LH and RH recruitment in anomia recovery is by calculating a lateralization index (LI) using fMRI data. The LI reflects hemispheric dominance in terms of the number of activated voxels observed in the context of a specific language task.[28] This index can express the relative contribution of either hemisphere to the processing of specific information, which can be linked to behavioral performance. Several studies have examined the relative contribution of either cerebral hemisphere to anomia recovery within the context of specific and intensive language therapy and by reference to principles of experience-dependent neuroplasticity, derived from animal research.[14, 15] These studies investigated the neurofunctional markers of adaptive plasticity and link right and left hemisphere performance to post-therapy behavior by correlating activation patterns to post-therapy scores on naming tasks.[29, 30]

Other studies used non-invasive brain stimulation techniques to modulate cortical excitability in either hemisphere, using repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS generates magnetic fields and this can either activate or inhibit neurons. rTMS inhibiting RH areas can significantly reduce speech-error production in non-fluent aphasia.[31, 32] Inhibiting the right pars triangularis (part of the

right inferior frontal gyrus) with rTMS improves naming accuracy and decreases naming latency, while activating the right pars opercularis decreases naming accuracy and improves naming latency.[32] With tDCS, a low current can be applied to the brain and, depending on the polarity, it can either enhance (anodal tDCS) or inhibit neural activity (cathodal tDCS) in a certain area. Studies using tDCS mostly combine tDCS with word-finding therapy and find an additional effect of tDCS on naming performance.[33, 34] In summary, rTMS/tDCS studies aim to modulate adaptive plasticity, either by inhibiting RH areas or enhancing LH areas.

In general, most of the fMRI literature on the recovery from anomia adopts a segregation approach in the analysis of fMRI activations. This is a within-area approach, based on activation changes occurring in isolation.[35] For example, a brain area found to be critical in successful naming is the left Brodmann area 22, which includes the superior temporal gyrus.[12, 36] Another perspective, the integration perspective, gathers brain activations within coherent networks supporting a specific behavior; for example, functional connectivity analysis can be used to study networks of language processing in healthy and brain-damaged populations.[37, 38]

In summary, research on the neural basis of anomia recovery has mostly focused on segregating brain areas whose activation is either associated with persistent anomia (i.e. paraphasia), reflecting maladaptive neuroplasticity, or with recovery (i.e. successful naming), reflecting adaptive neuroplasticity. Within this perspective, rTMS/tDCS has been used to modulate RH takeover by inhibiting RH areas, traditionally associated with maladaptive neuroplasticity, or by enhancing LH areas related to adaptive neuroplasticity. However, there is limited knowledge regarding the specific areas whose activation is either associated with the production of paraphasia or with successful naming.

The present study aims to examine maladaptive and adaptive neuroplasticity processes in the context of verb anomia recovery in aphasia. Three participants with non-fluent chronic aphasia were examined in the context of a picture-naming task during event-related fMRI scanning. Activation patterns related to the production of semantic paraphasia were obtained and compared with our previous study that focused on adaptive plasticity i.e. successful verb naming.[39] The relative contribution of the LH and RH to semantic paraphasia and successful naming is explored by calculating an LI.

MATERIALS AND METHODS

A. Experimental design

The fMRI blood oxygenation level-dependent (BOLD) responses associated with the production of semantic paraphasia produced in the context of verb naming were com-

pared to those related to successful verb naming. BOLD responses were collected in the context of an oral picture-naming verb task within an event-related fMRI paradigm.

B. Participants

Three male participants from the sample of Marcotte et al.,[40] diagnosed with moderate to severe Broca's aphasia, were examined. Inclusion criteria were: 1) a single LH stroke, 2) a diagnosis of moderate to severe aphasia, according to the Montreal-Toulouse battery,[41] 3) the presence of anomia in a standardized naming task,[42] 4) having French as their mother tongue, and 5) being right-handed prior to the stroke. Exclusion criteria were: 1) the presence of a neurological or psychiatric diagnosis other than stroke, 2) incompatibility with fMRI testing, or 3) a diagnosis of mild cognitive impairment or dementia prior to stroke, based on medical charts, speech-pathology reports, and information from the family. The study was approved by the Ethics Committee of the *Regroupement Neuroimagerie Québec* (Canada); all participants provided written informed consent.

Lesion location differed between the participants. Participant 1 (P1) presented a left fronto-parietal-temporal lesion, whereas Participants 2 (P2) and 3 (P3) presented a left fronto-temporal lesion (Figure 1).

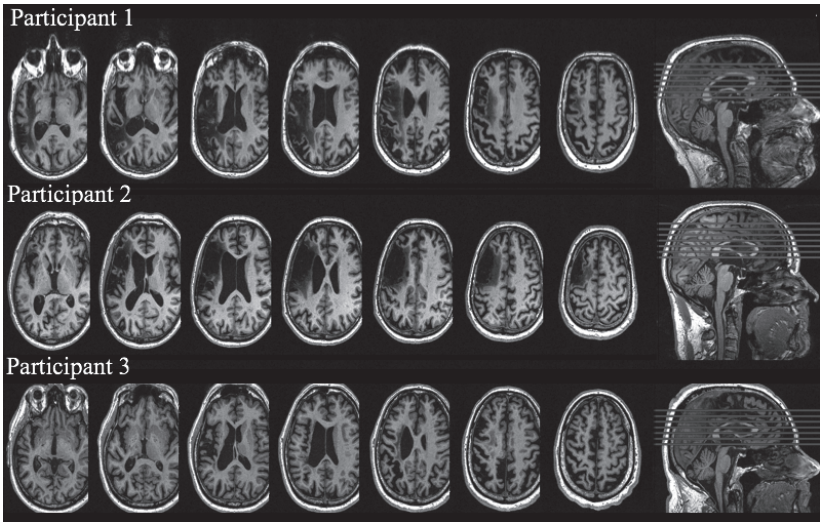

Figure 1. Lesion location for Participant 1, Participant 2 and Participant 3.

Table 1 presents demographic data; participants were comparable in terms of age and chronic status, and all had extended brain lesions in the left hemisphere (chi-square test: age, $p = 0.223$; months after stroke, $p = 0.199$; years of education, $p = 0.199$; lesion volume, $p = 0.199$).

Table 1. Demographic characteristics of the three participants (adapted from Durand[39]).

	Participant 1	Participant 2	Participant 3
Age (years)	67	67	66
Gender	Male	Male	Male
Months after stroke	72	54	241
Years of education	20	15	12
Lesion volume (cm^3)	167.84	117.84	84.77

C. Procedure

C.1 Language assessment

Aphasia profiles were determined with the Montreal-Toulouse 86.[41] To ensure stable performance, two baseline naming assessments were obtained before the fMRI study. This baseline assessment was used to select stimuli for the Semantic Feature Analysis therapy, in order to provide personalized therapy (for details see Marcotte et al.[40]). The selection was done on the basis of individual performance on the Snodgrass and Vanderwart items,[42] including object images, and ColorCards®,[43] including pictures depicting action verbs.

The present study focused on the ColorCards®[43] which included 120 pictures. A total of 80 pictures (60 incorrectly named verbs, and 20 correctly named verbs) were selected for the oral picture-naming task during the fMRI session. In addition, 20 digitally distorted images of a sub-set of these pictures were added as control stimuli.

C.2 fMRI session: stimuli and procedure

Participants underwent a practice session in the mock scanner to become accustomed to the scanner noise and environment during the fMRI session. During this session they were also trained to avoid head movements while naming the stimuli. The stimuli for the picture-naming task (ColorCards®) and the control stimuli (i.e. computerized distorted pictures) were projected on a white background by means of a series of mirrors, and in a random fashion. Each picture was presented for 4500 ms with an inter-stimulus interval ranging from 4500-8500 ms. Participants were asked to name the pictures representing verbs as accurately as possible and avoiding head movements. In the control condition, participants had to say 'BABA' when a computerized distorted picture was presented. Oral and event-related BOLD responses were collected.

C.3 Functional neuroimaging parameters

Images were acquired using a 3T MRI Siemens Trio scanner, with a standard 8-channel head coil. The image sequence was a T2*-weighted pulse sequence (TR = 2200 ms; TE = 30 ms; matrix = 64 × 64 voxels; FOV = 192 mm; flip angle = 90°; slice thickness = 3

mm; acquisition = 36 slides in the axial plane, with a distance factor of 25%, so as to scan the whole brain, including the cerebellum). A high-resolution structural image was obtained before the two functional runs using a 3D T1-weighted pulse sequence (TR = 2300 ms, TE = 2.91 ms, 160 slices, matrix = 256 × 256 mm, voxel size = 1 × 1 × 1 mm, FOV = 256 mm). The protocol was designed in an event-related fashion so that BOLD responses corresponding to each image could be identified.

D. Data analysis

Average response times and error rates were calculated for four sub-types of errors: semantic paraphasia, phonological paraphasia, neologism, and circumlocutions. Only semantic paraphasias were produced in a sufficient number to perform fMRI data analysis for all three participants. Therefore, the event-related fMRI responses to semantic paraphasia were analyzed following the same procedures as described by Marcotte et al.[40] and Durand.[39] Activation maps were obtained for each participant by subtracting BOLD responses in the control condition from those obtained in the trials where the answer provided was a semantic paraphasia. T-tests, performed on each voxel, were considered significant with a cluster size (k) ≥ 10 voxels and a p-value < 0.005. Individual activation maps, including significantly activated brain areas, were determined within the framework of the Talairach atlas[44] and transformed from Talairach space to the spatial coordinates in the Montreal Neurological Institute space.[45] BOLD responses on successful verb naming were examined in our previous study that included the same three participants.[39] In this previous study, BOLD responses in the control condition were subtracted from those obtained in the trials where the answer provided was a correct answer.

Furthermore, an LI[28] was calculated for each participant to estimate the relative contribution of the LH and the RH to the production of semantic paraphasia and successful naming, respectively. Regarding successful naming, data from Durand[39] were used. We applied Lehéricy's algorithm,[28] as follows: (LH-RH)/(LH+RH), by which a positive LI corresponds to a LH dominant contribution; a strong left lateralization is represented by an LI ranging from 0.5-1.0, and a weak left lateralization is represented by an LI ranging from 0.25-0.5. A negative LI corresponds to a predominantly RH contribution; a strong right lateralization is represented by an LI ranging from -1.0 to -0.5, and a weak right lateralization is represented by an LI ranging from -0.5 to -0.25. An LI ranging from -0.25 to 0.25 represents a symmetric contribution of the left and right hemispheres to processing.

RESULTS

A. Behavioral results

Average response times were calculated for paraphasia production; however, due to technical issues these data were not available for analysis. For the 80 pictures, Table 2 presents the error rates and the type of paraphasia produced by each participant during the event-related fMRI study. P1 produced 60 semantic paraphasias and 20 correct responses; P2 produced 15 semantic paraphasias, 32 circumlocutions and 33 correct responses; and P3 produced 47 semantic paraphasias and 33 correct responses. Only semantic paraphasias were produced in a sufficient number to perform fMRI data analysis for all three participants.

Table 2. Error rates and the type of paraphasia produced by each participant.

	Participant 1	Participant 2	Participant 3
Semantic paraphasia	60	15	47
Phonological paraphasia	0	0	0
Neologism	0	0	0
Circumlocution	0	32	0

B. fMRI results

B.1 Single-subject brain activation maps

Brain activation maps corresponding to maladaptive plasticity, i.e. production of semantic paraphasia, in each participant are summarized in Table 3A-C. In P1, the production of semantic paraphasia was observed concurrently with significant activation of the precentral gyrus bilaterally, the left superior frontal gyrus (SFG), the inferior frontal gyrus (IFG) bilaterally, cerebellum (culmen bilaterally, right cerebellar tonsil), the left middle frontal gyrus (MFG), the left brain stem (pons), the left postcentral gyrus, the left fusiform gyrus, the right posterior cingulate cortex, and the right superior temporal gyrus (STG). In P2, the production of semantic paraphasia was observed concurrently with significant activation of the left thalamus (ventral lateral nucleus), the left inferior temporal gyrus (ITG), the cerebellum (left inferior semi-lunar lobule, right tuber), the right cuneus, the right MFG, the right IFG, the right STG, the right precuneus, the right precentral gyrus, the right middle temporal gyrus (MTG), and the right posterior cingulate cortex. Finally, in P3, the production of semantic paraphasia was observed concurrently with significant activation of the MTG bilaterally, the IFG bilaterally, the left superior parietal lobule, the left inferior parietal lobule, the right precentral gyrus, the right cingulate gyrus, the right SFG, the right putamen, the right MFG, and the right insula.

Table 3A. Participant 1: significantly activated areas associated with the production of semantic verb paraphasia.

Left hemisphere							Right hemisphere						
		Results SPM			T-score	Cluster			Results SPM			T-score	Cluster
Region	BA	X	Y	Z		size	Region	BA	X	Y	Z		size
Frontal lobe, precentral gyrus	*4*	*-16*	*-28*	*76*	*3.00*	*43*	**Limbic lobe, posterior cingulate cortex**	29	2	-50	8	3.89	74
Frontal lobe, superior frontal gyrus	6	-20	2	76	2.97	15	**Cerebellum, culmen**		44	-50	-40	3.74	14
Frontal lobe, inferior frontal gyrus	47	-36	22	-18	2.93	18	**Frontal lobe, precentral gyrus**	4	66	-2	18	3.70	34
Cerebellum, culmen		-34	-50	-22	4.03	163	**Cerebellum, cerebellar tonsil**		26	-44	-44	3.47	19
Frontal lobe, middle frontal gyrus	47	-46	40	-12	3.46	38	**Frontal lobe, inferior frontal gyrus**	47	38	22	-20	3.37	12
Frontal lobe, middle frontal gyrus		-62	10	36	3.07	23	***Temporal lobe, superior temporal gyrus***	*22*	*70*	*-34*	*12*	*5.92*	*332*
Brainstem, pons		*-4*	*-22*	*-36*	*4.92*	*32*	***Frontal lobe, precentral gyrus***	*6*	*66*	*-12*	*40*	*4.07*	*155*
Frontal lobe, postcentral gyrus		-58	-10	50	4.72	132							
Occipital lobe, fusiform gyrus		-44	-76	-20	4.10	53							

Table 3B. Participant 2: significantly activated areas associated with the production of semantic verb paraphasia.

Left hemisphere							Right hemisphere						
	Results SPM				T-score	Cluster		Results SPM				T-score	Cluster
Region	BA	X	Y	Z		size	Region	BA	X	Y	Z		size
Thalamus, ventral lateral nucleus		-14	-10	4	3.20	10	**Occipital lobe, cuneus**	19	18	-86	34	3.15	19
Temporal lobe, inferior temporal gyrus	19	-48	-76	-6	8.64	5520	**Frontal lobe, middle frontal gyrus**	6	40	0	44	3.11	22
Cerebellum, inferior semi-lunar lobule		-18	-70	-48	4.66	338	**Frontal lobe, inferior frontal gyrus**	13	34	16	-22	3.06	33
							Temporal lobe, superior temporal gyrus	22	58	-8	2	2.96	17
							Parietal lobe, precuneus	7	16	-74	56	2.94	11
							Frontal lobe, precentral gyrus	4	16	-36	72	2.93	13
							Temporal lobe, middle temporal gyrus	22	64	-36	2	2.90	23
							Limbic lobe, posterior cingulate cortex		10	-70	12	2.86	22
							Occipital lobe, cuneus	18	12	-86	18	2.85	16
							Cerebellum, tuber		*50*	*-56*	*-36*	*5.36*	*679*
							Temporal lobe, superior temporal gyrus	*22*	*56*	*12*	*-6*	*5.28*	*141*
							Temporal lobe, middle temporal gyrus	*21*	*66*	*-50*	*2*	*4.21*	*91*

Table 3C. Participant 3: significantly activated areas associated with the production of semantic verb paraphasia.

Left hemisphere							Right hemisphere						
		Results SPM			T-score	Cluster			Results SPM			T-score	Cluster
Region	BA	X	Y	Z		size	Region	BA	X	Y	Z		size
Temporal lobe, middle temporal gyrus	39	-62	-60	8	2.90	16	**Frontal lobe, precentral gyrus**	6	48	0	48	3.28	95
Frontal lobe, inferior frontal gyrus	*45*	*-54*	*20*	*18*	*6.90*	*16933*	**Limbic lobe, cingulate gyrus**	24	6	4	30	3.26	25
Parietal lobe, superior parietal lobule	*7*	*-36*	*-72*	*46*	*5.67*	*510*	**Frontal lobe, superior frontal gyrus**	9	18	48	32	3.10	53
Parietal lobe, inferior parietal lobule	40	-50	-52	48	3.74	169	**Lentiform nucleus, putamen**		30	2	-10	3.00	25
							Frontal lobe, inferior frontal gyrus	45	64	12	20	2.99	25
							Frontal lobe, middle frontal gyrus		52	34	16	2.92	36
							Insula		38	22	-4	4.40	745
							Temporal lobe, middle temporal gyrus	21	48	8	-40	3.41	11

Table 4. Participant 1, 2 and 3: significantly activated areas associated with successful verb naming (adapted from Durand[39]).

	Left hemisphere							Right hemisphere						
			Results SPM			T-score	Cluster			Results SPM			T-score	Cluster
	Region	BA	X	Y	Z		size	Region	BA	X	Y	Z		size
Participant 1	Middle frontal gyrus	6	-38	0	62	4.07	608	Superior frontal gyrus	6	10	2	64	4.54	608
	Precentral gyrus	4	-56	-8	50	4.64	129	Precentral gyrus	6	66	-12	40	4.21	506
	Precentral gyrus	4	-16	-28	72	4.3	111	Middle frontal gyrus	6	28	-6	54	3.98	153
	Pons		-2	-22	-36	4.87	57	Superior temporal gyrus	22	70	-36	12	4.01	64
								Middle temporal gyrus	21	70	-32	4	3.64	64
Participant 2	Middle occipital gyrus	18	-48	-76	-8	7.13	3404	Middle frontal gyrus	6	2	-2	70	6.33	637
	Lingual gyrus	18	-10	-72	-8	6.14	3404	Cerebellum, tuber		50	-56	-36	5.84	83
	Superior parietal lobule	7	-6	-66	60	4.23	116	Fusiform gyrus	37	45	-56	-24	3.9	83
	Precuneus	7	-15	-72	45	3.88	116	Cerebellum, inferior semi-lunar lobule		12	-70	-48	4.29	74
								Superior temporal gyrus	22	54	14	-6	4.68	54
								Superior frontal gyrus	9	2	52	40	3.91	22
								Middle temporal gyrus	21	66	-50	2	3.8	22
Participant 3	Inferior frontal gyrus	45	-54	22	18	6.05	2028	Sulcus callosomarginalis	8	10	18	48	5.82	1858
	Inferior frontal gyrus	44	-40	10	20	5.84	2028	Middle frontal gyrus	8	6	32	36	4.75	1858
	Middle frontal gyrus	6	-46	12	48	5.25	2028	Middle frontal gyrus	8	36	20	48	3.66	266
	Middle frontal gyrus	6	-22	14	44	4.67	1858	Caudate nucleus		18	-20	22	4.17	205
	Middle frontal gyrus	6	-28	48	18	4.68	449	Inferior temporal gyrus	37	48	-56	-14	4.07	17
	Superior frontal gyrus	9	-8	50	30	3.75	449							
	Superior parietal lobule	7	-36	-72	46	5.17	167							

Table 4 summarizes brain activation maps corresponding to adaptive plasticity (i.e. successful naming) in each participant, adapted from Durand.[39] Successful naming was observed concurrently with significant activation of the MFG bilaterally and the precentral gyrus bilaterally. For the LH, successful naming was observed concurrently with significant activation of the IFG, the SFG, the middle occipital gyrus, the lingual gyrus, the superior parietal lobule, the precuneus, and the pons. For the RH, successful naming was observed concurrently with significant activation of the STG, the MTG, the ITG, the cerebellum (tuber and inferior semi-lunar lobule), the fusiform gyrus, the sulcus callosom arginalis, and the caudate nucleus.

A comparison was made between brain activation maps associated with semantic paraphasia and those associated with successful naming. In all participants, brain activation maps associated with semantic paraphasia and those associated with successful naming included a number of common significant activations. These common significant activations are highlighted in Table 3A-C. In P1, the areas significantly activated with both semantic paraphasia and successful naming included the precentral gyrus bilaterally, the left brainstem (pons), and the right STG. In P2, the areas significantly activated with both semantic paraphasia and successful naming included the cerebellum (tuber), the right STG, and the right MTG. Finally, in P3, the areas significantly activated with both semantic paraphasia and successful naming included the left IFG, and the left superior parietal lobule.

B.2 Lateralization indexes

Table 5 presents the LI for the brain activation maps related to maladaptive plasticity (production of semantic paraphasia) and adaptive plasticity (successful naming) for each participant.

Table 5. Lateralization indexes related to maladaptive plasticity, i.e. production of semantic paraphasia, and adaptive plasticity, i.e. successful naming, for each participant. A lateralization index ranging from -0.25 to 0.25 represents a symmetric contribution of the left and right hemispheres to processing (Participant 1), whereas a positive value above 0.25 indicates a predominant LH contribution to processing (Participant 2 and 3) [28].

	Participant 1	Participant 2	Participant 3
Brain activation map for semantic paraphasia	-0.11	0.69	0.89
Brain activation map for successful naming	-0.21	0.76	0.36

The three participants showed bilateral significant activations for both semantic paraphasia and successful naming. Regarding the production of semantic paraphasia, two distinct patterns were observed. Whereas P1 presented a symmetric activation pattern

(-0.11), P2 and P3 showed a strong predominantly LH activation (0.69 and 0.89, respectively). Regarding successful verb naming, P1 showed a symmetric activation pattern (-0.21), P2 showed a strong predominantly LH activation (0.76), and P3 showed a weak predominantly LH activation (0.36).

DISCUSSION

The present study aimed to explore maladaptive plasticity, defined as the production of a semantic paraphasia, in oral verb naming. Three participants with non-fluent chronic aphasia were examined in the context of a picture-naming task during event-related fMRI scanning. Activation patterns related to the production of semantic paraphasia were obtained and compared to our previous study on adaptive plasticity i.e. successful verb naming.[39] For each participant, the relative contribution of the RH and LH to the production of semantic paraphasia and successful verb naming were determined by calculating an LI.

Results show that the production of semantic paraphasia was associated with the significant activation of right and left hemisphere areas in all three participants. All of these areas are reported to sustain normal language processing in healthy adults[46] and particularly verb production.[6-11] The recruitment of these areas may reflect the attempt to find the correct target verb; however, the attempt to compensate for the system's damaged components is not sufficient and leads to a semantic paraphasia that is in some way related to the target word. In addition, the production of semantic paraphasia was associated with specific activation patterns in all participants. This may reflect the impact of individual factors such as lesion location and extension, time elapsed post-stroke, age and education level, all of which have been shown to influence language representation and processing.[47-51] Also, specificities in the mechanisms underlying the production of semantic paraphasia between participants may explain these differences. For example, research on cognitive mechanisms underlying the production of semantic paraphasia shows that these may result from impaired phonological processing, or impaired semantic processing, or a combination of both impairments.[5] In the present study, we did not examine the degree of relative impairment at either of these processing levels in each participant. Therefore, we cannot exclude the possibility that the mechanisms underlying the production of semantic paraphasia may have differed between participants; this may explain why each participant showed specific activations in relation to the production of paraphasia.

The present study also compared the activation patterns related to the production of semantic paraphasia to our previous study on adaptive plasticity i.e. successful verb

naming.[39] In each participant, a number of common activations were observed for semantic paraphasia and successful naming. For P1 these included the precentral gyrus bilaterally, the left brainstem (pons) and the right STG; for P2 these included the right cerebellum (tuber), the right STG and the right MTG; and for P3 these included the left IFG and the left superior parietal lobule.

Interestingly, also these areas are known for their contribution to language processing in healthy adults and, particularly, to sustain verb production. Some of these areas are known to be involved in lexico-semantic processing. The precentral gyrus is known for its role in action semantics[9-11] and the left precentral gyrus is part of a well-known left-lateralized semantic processing circuit.[52-54] The left IFG is involved in lexico-semantic processing[55] and significant activation of the left superior parietal lobule is related to verb production.[7] Further, the right homologue of the left STG is involved in verb production.[7] Besides these areas involved in lexico-semantics, there are common areas for semantic paraphasia and successful naming that are involved in phonological encoding, articulation and motor speech. The left IFG and the left STG are involved in phonological processing.[56, 57] The left IFG, left MTG and cerebellum, together with the primary motor cortex (part of the precentral gyrus), support articulatory planning in speech.[21, 57-59] Regarding the left brainstem (pons) and the cerebellum (tuber), they are part of a cerebro-cerebellar loop, sustaining articulation and motor speech stages of word production.[60, 61]

The finding that our three participants showed common significant activations during both semantic paraphasia and successful naming may again reflect an attempt of the system to find the correct target verb; sometimes the attempt is successful, other times it is not. The production of semantic paraphasia may represent a non-efficient system's attempt to compensate for its damaged components, which leads to the selection of an error production that is in some way related to the target word. Conversely, successful naming may reflect a function of the spared tissue or an adaptive compensation for the damaged language components, leading to activation of the correct target word. Moreover, the finding of common significant activations during both semantic paraphasia and successful naming also suggests that segregation of brain areas provides only a partial view of the neural basis of verb anomia and successful verb naming, and indicates the need to involve network approaches which better capture the complexity of neuroplasticity mechanisms in anomia recovery.

Concerning the lateralization of processing, the contributions of the LH and RH to semantic paraphasia and/or to successful naming are still not totally clear. The LI results of the present study show that both hemispheres contribute to the production of semantic paraphasia and successful naming. RH activation is not exclusively related to

the production of semantic paraphasia, but can also be related to successful naming. Therefore, in the present study, RH activation may correspond to efficient compensation in the context of adaptive plasticity processes. This is in line with studies reporting RH activation in the context of successful naming in persons with aphasia[17] and also in healthy participants.[22]

The finding that the extent of RH recruitment differed between the three participants might be attributed to lesion size.[12, 26] Larger lesions (associated with poor recovery of language functions) are associated with RH contribution, while in the case of small LH lesions the left perilesional cortex can sustain language recovery. This mechanism is supported by the present data. P1 presents a large lesion and shows a symmetric activation pattern during both semantic paraphasia and successful naming. In contrast, the LI of P2 and P3 reflects predominantly LH activation in the presence of smaller LH damage and smaller error rates. The observation of a larger number of semantic verb paraphasia in P1 can also be related to RH semantic processing abilities. Therefore, it is possible that the RH has access to underspecified semantic representations[24] which may favor the production of a semantic paraphasia. However, RH activation in the context of aphasia recovery may reflect the system's attempt to compensate for its damaged components and, to some extent, support access to the correct target word. Therefore, in these three participants the production of semantic verb paraphasia may reflect an attempt to reach the target in the recovery process.

In summary, these results show that, while the global activation pattern differs between the participants, the activation patterns related to maladaptive neuroplasticity and adaptive neuroplasticity comprise a number of common areas. Also, the relative contribution of the left and right hemisphere to maladaptive and adaptive plasticity is not totally clear. This finding challenges the dichotomic distinction between the maladaptive and adaptive roles of the right and left hemisphere, respectively. The present results show that RH recruitment may be associated with adaptive plasticity mechanisms supporting recovery from anomia. Therefore, these findings raise questions regarding the generalizability of rTMS/tDCS studies reporting the advantages of selectively inhibiting the RH homologue of Broca's area to trigger anomia recovery.[31-34] The present findings suggest that inhibiting these areas may, at least in some cases, prevent the expression of the adaptive potential of the RH to support anomia recovery and/or abort the emergence of semantic strategies that may contribute to attenuate the effects of anomia in everyday communication.

The present results support a less dichotomic perspective with regard to the contribution of the right and left hemisphere to recovery from anomia and indicate the

importance of adopting a wider perspective when examining the neural basis of anomia recovery. In particular, functional connectivity approaches offer an interesting alternative to the segregation perspective, as they allow to consider the dynamic changes that occur within a specific brain network, which may be composed of a similar set of areas. The functional connectivity approach highlights changes in network configuration and activity, depending on a variety of factors, such as complexity level and type of task. Future functional connectivity studies on the neural basis of anomia recovery may help unravel the complex mechanisms underlying neuroplasticity in anomia recovery.

A limitation of the present study is the small number of participants and the fact that all of them were male. However, single-case studies provide important information regarding the variety of idiosyncratic activation patterns in paraphasia and successful naming. Nevertheless, larger samples, including males and females, need to be examined to further elucidate the role of right hemisphere areas and circuits in the adaptive or maladaptive mechanisms that sustain anomia recovery.

Conclusion

The present study explored maladaptive plasticity in persistent verb anomia by analyzing activation patterns associated with semantic verb paraphasia production in three male participants with chronic non-fluent aphasia. The results show that activation patterns associated with paraphasia production differ across the three participants. This reflects individual factors such as lesion location, time post-onset, as well as the nature of the underlying processing deficits in the context of anomia. The present study also compared the activation patterns related to the production of semantic paraphasia to our previous study on adaptive plasticity i.e. successful verb naming.[39] Interestingly, our three participants showed common significant activations during both semantic paraphasia and successful naming. Finally, the data show that both the LH and RH are related to the production of semantic paraphasia, thereby questioning the idea of a maladaptive role of the RH. Our findings have implications for future studies aiming to inhibit or activate specific areas in the context of rTMS/tDCS, and suggests that the neural basis of paraphasia and successful naming is not mutually exclusive, but may reflect dynamic processes within a relatively limited set of contributing areas.

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CHAPTER 8

General discussion

A main challenge in aphasia rehabilitation is to improve our understanding of the neural basis of spontaneous neurological recovery and to provide treatments that may enhance behavioral recovery, beyond what can be expected from spontaneous neurological recovery processes alone.[1, 2] This thesis aims to improve our understanding of neuroplasticity in post-stroke aphasia, and explores whether neuroplasticity can be promoted with transcranial Direct Current Stimulation (tDCS).

Since 2008, there has been an increase in published studies reporting a positive effect of tDCS in treating post-stroke aphasia.[3-6] tDCS is a non-invasive neurostimulation technique with limited side-effects and easy to apply in clinical care, therefore it has become a popular technique in neurorehabilitation. However, many studies reporting positive tDCS effects have methodological limitations such as small sample size. Mostly they are performed in patients in the chronic phase, which is beyond the phase of spontaneous recovery after stroke. It is important to investigate the potential effects of tDCS in the sub-acute phase, since in this phase most spontaneous neurological recovery takes place and most treatment is provided. Therefore, the potential effect of tDCS in the sub-acute phase is clinically of interest. Further, since 2016 studies have been published which report a lack of reproducibility of previously reported positive effects of tDCS.[7, 8] Besides the fact that the efficacy of tDCS still needs to be established it should be noted that insights in the mechanisms involved in tDCS are limited. Even studies reporting positive effects, have emphasized that the impact of several individual parameters is largely unknown, such as the optimal electrode configuration, lesion characteristics and the underlying language deficits.[9] Therefore, tDCS is described as a potential tool in aphasia rehabilitation, although the effectiveness, the underlying mechanisms and the impact of individual parameters are so far not well understood.

The primary aim of this thesis is to investigate the effect of tDCS in post-stroke sub-acute aphasia. In addition, the effectiveness of different tDCS electrode configurations for aphasia treatment is evaluated, namely tDCS over the left inferior frontal gyrus (left-IFG) and over the left superior temporal gyrus (left-STG). In healthy subjects, we investigated tDCS over the right cerebellum and its' effects on language performance. Finally, two studies looked into inter-individual variability in neuroplasticity, 1) we studied the effects of the Brain-Derived Neurotrophic Factor (BDNF) polymorphism on aphasia recovery, and 2) we used neuroimaging data to study individual brain activation maps, and segregated cortical areas contributing to either correct naming or naming errors. We addressed our study aims by performing a double-blind randomized-controlled trial (RCT), two within-subject cross-over studies, a prospective cohort study and a multiple case study. In this chapter, I will recapitulate the main findings of our studies, discuss

the main findings and relate it to previous literature. I will finish with methodological considerations, clinical implications and future perspectives.

MAIN FINDINGS

Effect of tDCS in post-stroke sub-acute aphasia

To investigate the effect of tDCS in post-stroke sub-acute aphasia, we performed a multicenter double-blind RCT with two groups and six months follow-up (**chapter 2 and chapter 3**). In this RCT, 58 patients with aphasia were included within three months post stroke. Embedded in a regular rehabilitation program, participants received two separate weeks in which word-finding therapy was combined with either active tDCS (experimental group) over the left-IFG or sham tDCS over the same region (control group). The primary outcome measure was picture naming performance on the Boston Naming Test. Other outcome measures were picture naming performance on trained and untrained items, verbal communication, quality of life and participation. This design allowed us to study the effectiveness of tDCS as an add-on treatment to word-finding therapy, compared to word-finding therapy alone. Our major finding is that whereas both the experimental group and the control group improved on the primary outcome measure, there was no significant difference in improvement between the groups over the intervention period or follow-up period. For the other outcome measures, there were also no significant differences between the groups. Therefore there was no significant contribution of tDCS to language outcome. With regards to treatment tolerance and side-effects, treatment was well-tolerated and during treatment the only side-effects being reported were a tingling sensation and headache, which is in line with side-effects reported in other studies.[10, 11]

Different tDCS electrode configurations for aphasia treatment

To investigate the effects of different electrode configurations, two within-subject cross-over studies were performed: one in chronic patients with aphasia (**chapter 4**) and one in healthy subjects (**chapter 5**). In **chapter 4**, anodal tDCS over the left-IFG and anodal tDCS over the left-STG were compared within 13 individuals with post-stroke chronic aphasia. We compared these two active tDCS configurations with sham-tDCS, in three single sessions. Outcome measures included picture naming performance on trained and untrained items. Besides, we were also interested in choosing an optimal configuration per individual, based on a pre-set criterion for proportional improvement in a single therapy session. On a group level, participants showed better performance on trained items in the left-IFG configuration condition. This is in line with several other studies showing a positive effect of anodal tDCS over the left-IFG.[6, 12, 13] Choosing an optimal configuration per individual could only be guided by performance on trained items and

was not possible for all patients. Untrained items could not be used as there were no improvements in performance after single sessions. As less improvement on untrained items compared to trained items[3, 14] can be assumed, it may be unrealistic to expect an effect on untrained items in single therapy sessions. Interestingly, three patients showing better performance on trained items during the left-IFG configuration were diagnosed with non-fluent aphasia. This observation is of interest, as it is hypothesized that frontal stimulation may be useful in the case of non-fluent aphasia while temporal stimulation may be more useful in the case of fluent aphasia.[3, 4]

Interestingly, in the last years, the cerebellum has been associated not only with motor control, but also with cognitive processing including language processing.[15-17] Further, because of the complicated interplay of both hemispheres in aphasia recovery, some authors propose to find other potential targets for brain stimulation, such as the cerebellum.[2, 18] In **chapter 5**, we aimed to replicate the results of a between-subject study design from Pope and Miall[19] showing that cathodal tDCS over the right cerebellum in healthy participants reduces verbal reaction time on a verb generation task. These authors speculated that cathodal cerebellar stimulation over the right cerebellum leads to disinhibition of prefrontal regions. This in turn leads to the release of cognitive resources which enhances performance on a verb generation task, in terms of shorter verbal reaction times. In our study, we failed to replicate this effect of tDCS on verb generation task performance. However, in our within-subject design we found an order effect, such that participants who received cathodal tDCS during the first session, showed longer verbal reaction times during the second session. We can explain this finding by a possible negative consolidation effect, such that the right cerebellum plays a role in learning and inhibition of right cerebellar involvement may reduce the learning rate. This tDCS-induced negative consolidation effect has also been described in tDCS and motor studies.[20-22] In **chapter 5**, we discuss and relate our findings with motor learning studies, however the involvement of the cerebellum in language learning is less clear and remains to be studied. Our results in **chapter 5** therefore suggest that tDCS over the cerebellum warrant further exploration in healthy subjects, including studying long term effects, before undertaking clinical studies in post-stroke aphasia.

Inter-individual variability in neuroplasticity

To study inter-individual variability in neuroplasticity, we have performed a prospective cohort study (**chapter 6**) and a multiple case study (**chapter 7**). In **chapter 6**, we compared patients having a Val66Val genotype (non-carriers of the BDNF polymorphism) with patients having a Val66Met genotype (carriers of the BDNF polymorphism). The BDNF polymorphism relates to low levels of BDNF secretion, which is associated with less learning capacity in healthy subjects and a less favorable outcome after stroke.[23, 24]

So far, the influence of the BDNF polymorphism on aphasia recovery has not been investigated. We included 53 stroke patients with post-stroke sub-acute aphasia, who were enrolled in an inpatient stroke rehabilitation program and received regular aphasia treatment. Verbal communication and picture naming were assessed at admission and at discharge. Both groups improved, with no significant differences in improvement on verbal communication or picture naming. This study therefore suggests that the BDNF polymorphism does not influence sub-acute aphasia treatment outcome.

The neuroimaging study in **chapter 7** uses individual brain activation maps to explore maladaptive plasticity in three participants with post-stroke chronic non-fluent aphasia. Brain activation maps associated with naming errors (i.e. semantic paraphasias) occurring within an oral verb picture-naming task were identified with an event-related functional Magnetic Resonance Imaging (fMRI) paradigm. These maps were compared with those obtained in a previous study examining adaptive plasticity (i.e. successful naming) in the same participants. Results showed that there was individual variability in brain activation patterns; one participant, who had a large lesion, produced more naming errors and the activation patterns were more bilateral, compared to the other two participants with smaller lesions. Interestingly, our three participants showed common significant activations during both naming errors and successful naming. This finding suggests that the segregation of brain areas provides only a partial view of the neural basis of naming errors and successful naming. Therefore, it indicates the importance of network approaches which may better capture the complexity of maladaptive and adaptive neuroplasticity mechanisms.

INTERPRETATION

The main study of this thesis showed that there is no effect of tDCS as an add-on treatment to word-finding therapy in sub-acute aphasia. There is a general agreement that spontaneous recovery is more present in the first three months after stroke, and therefore we applied tDCS, combined with word-finding therapy, within three months post stroke with the aim to support spontaneous neural recovery. In line with our findings, the study of Polanowska et al.[25] also reported no effect of tDCS in sub-acute aphasia. They emphasized that in the sub-acute phase spontaneous recovery processes are rather high compared to the more stable language functioning in the chronic phase, and perhaps in the sub-acute phase tDCS may not further facilitate left hemisphere (LH) activity above these spontaneous neurological recovery processes.[26, 27]

Although applying tDCS within three months post stroke may be too early to be effective, several other factors may explain a lack of tDCS effect in our main study. The applied

tDCS electrode configuration may be a critical factor. Across studies, there is variability in either targeting the LH or right hemisphere (RH), and variability in targeting specific cortical areas within a hemisphere.[5, 28-31] In general, targeting the LH or RH with tDCS is based on the concept of *interhemispheric imbalance*. This means that the undamaged hemisphere inhibits the electrophysiological activity of the damaged hemisphere, and thereby it reduces the capacity of the damaged hemisphere to recover. In aphasia recovery,[32] this concept implies that a lesioned LH, which is generally the dominant hemisphere for language processing, is suppressed by the RH. Several neuroimaging studies have emphasized the important role of the LH in aphasia recovery.[26, 32, 33] The exact role of the RH in aphasia recovery is less clear, some studies suggest that RH activation is adaptive in aphasia recovery while other studies suggest that it is maladaptive. In general, there is more support for a crucial role of the LH such that its' recruitment is assumed to be adaptive in aphasia recovery. Therefore, most studies applying tDCS in aphasia aim to promote recruitment of LH areas either by applying anodal tDCS over the LH or cathodal tDCS over the RH.

The application of anodal tDCS over the LH was not effective in our main study, however, interestingly, a recent meta-analysis[34] reported a small and significant effect of inhibiting repetitive Transcranial Magnetic Stimulation (rTMS) over the RH in sub-acute aphasia. One could speculate that inhibiting the RH may be a more suitable approach for treating sub-acute aphasia than using excitatory stimulation over the LH, i.e. applying anodal tDCS over the LH, as performed in our main study. Further, a differential effect on regions within a single hemisphere may occur. One rTMS study found that inhibition of one specific area in the RH is related with increased naming performance in patients with aphasia, while inhibition of another specific area in the RH leads to decreased naming performance.[35] Therefore, choosing a tDCS electrode configuration in aphasia rehabilitation goes beyond the choice of either targeting the LH or RH; it also requires to take into account the complex interplay of several areas within a hemisphere.

Some studies propose to choose a tDCS electrode configuration on an individual basis.[3, 4, 36, 37] These studies suggest that a 'one-fits-all approach' which is used by the majority of tDCS studies, i.e. applying the same electrode configuration in all participants, does not take into account individual parameters such as lesion size or site. Lesion size or site may influence language system reorganization; in chapter 7, we described a multiple case series and found that one case with a large lesion showed a more bilateral brain activation pattern compared with those who had smaller lesions. Lesion size/site may also determine the optimal tDCS electrode configuration per individual. So far, not many studies have discussed these individual parameters. Regarding lesion size, some studies suggest that facilitation of LH activity may not be possible in the case of a large

LH lesion.[9, 37] In case of large lesions in the LH, the capacity for recovery in perilesional areas may be insufficient, consequently recovery may be dependent on RH activity.[38] As such, inhibiting the RH may be harmful in the case of a large LH lesion,[9] and perhaps these patients may actually benefit from applying anodal tDCS over the RH.[39]

Only one research group has taken into account lesion site by using neuroimaging; they used an fMRI naming paradigm to determine tDCS electrode configurations per individual.[3, 4] The brain area with the highest activation during correct naming was chosen to be the target area for tDCS. Interestingly, frontal areas were the stimulation target for people with non-fluent aphasia whereas temporal areas were the stimulation target in the case of fluent aphasia.[3, 4] Therefore these authors speculated that frontal stimulation may be useful in the case of non-fluent aphasia, while temporal stimulation may be more useful in the case of fluent aphasia. However, in chapter 4 we only partly confirmed this hypothesis, as three out of six patients with non-fluent aphasia responded to frontal stimulation, and none of the patients with fluent aphasia responded to posterior stimulation. Perhaps also other factors than aphasia type play a role in inter-individual variability in response to frontal or temporal stimulation. One could also argue that our single session paradigm was not sufficient to confirm previous hypotheses. To summarize, multiple factors may play a role in choosing an optimal tDCS electrode configuration in aphasia treatment, and probably configurations may be chosen at an individual basis.[36, 37]

Besides lesion characteristics and aphasia type, other individual parameters may influence the effectiveness of tDCS. From motor studies it is found that BDNF mediates the effect of tDCS on long term potentiation,[40, 41] and therefore individual variability in BDNF secretion is also proposed to be a factor which influences tDCS effectiveness. Carriers of the BDNF polymorphism may respond differently to tDCS than non-carriers, as carriers have less BDNF secretion. Further, the BDNF polymorphism is thought to play a role in stroke outcome.[23, 24] However, studies on BDNF polymorphism and aphasia outcome are lacking. Our results in chapter 6 do not show a significant contribution of the BDNF polymorphism on sub-acute aphasia rehabilitation outcome. Whether the BDNF polymorphism influences aphasia outcome, and specifically determines variability in tDCS response remains to be studied in future research.[42]

METHODOLOGICAL CONSIDERATIONS

Study design

Our RCT in chapter 3 was designed to study an add-on effect of tDCS on word-finding treatment in the sub-acute phase. We hypothesized that early treatment interacts with

spontaneous recovery and that tDCS may enhance this effect. However, the optimal timing of aphasia treatment is still under discussion,[43] and so based on our design we cannot investigate the effect of our word-finding treatment itself above spontaneous recovery processes. The intensity and duration of the provided tDCS intervention is another potential limitation as intensity and duration may be important determinants for the effect of treatment.[44] Previous tDCS studies reporting a positive effect used a similar intensity (5x per week) and duration (1-2 weeks) as we did and we wanted to stay close to the intensity and duration of these earlier studies.[3, 13, 14]

A limitation of our design in chapter 4, is that an individualized tDCS configuration based on a single session, is not necessarily the optimal configuration for multiple sessions. For future studies it will be interesting to study whether performance in a single session is a predictor for treatment effects after 1 week, but also to study for which patients it is possible to determine an optimal configuration after a single session. In chapter 5 we wanted to replicate the results from Pope and Miall.[19] We have used a within-subject design while Pope and Miall have used a between-subject design. A within-subject design was chosen because we expected that the effects would be larger due to a reduction in individual variability between the conditions. However, our different study design could also interfere with the replication of the results because the contrast between the conditions may become lower due to practice effects. The lack of replication of the results may suggest that the experimental condition is more important in tDCS studies than assumed.[8]

Baseline and outcome measures

Baseline tests in chapter 3 and 4 were limited as we did not collect lesion information for all participants. As discussed earlier, lesion characteristics may be an important factor to study individual variability in response to tDCS. Further, baseline tests did not include nonlinguistic cognitive functioning assessments, whereas cognitive functioning, such as executive functioning or monitoring ability are important predictors for word-finding treatment effects in aphasia.[45] However, many cognitive tests include a language component and therefore it remains a challenge to test patients with aphasia with a comprehensive cognitive test battery.[46]

Naming was used as an outcome measure in several studies (chapter 3, 4, 6, 7). Typically, the primary outcome measure for word-finding therapy studies in aphasia is naming accuracy. It reflects word retrieval as well as word production abilities, and also naming is positively correlated to overall language ability.[47] However, naming can be limited with regards to the assessment of the underlying linguistic deficits. In our studies naming was scored as either correct or incorrect, whereas underlying deficits, such as semantic

access problems or phonological output problems, were not assessed with this scoring system. A more detailed linguistic assessment would have given more insights in the underlying naming deficits of our participants.

So far, most tDCS and aphasia studies have only included naming as an outcome measure, whereas it has also been emphasized to assess more clinically relevant outcome measures[48] such as verbal communication, participation and quality of life. A strength of our main study in chapter 3 is that we included these outcome measures.

CLINICAL IMPLICATIONS

The results of our main study show that tDCS is a user-friendly tool in the clinic with limited side-effects, however we found that tDCS, when applied within three months post-stroke, is not effective as an add-on treatment in aphasia rehabilitation aimed to train word-finding. One may argue that our 'one-fits-all approach' (i.e. using one electrode configuration for all participants) may not be effective in stroke rehabilitation, as there is a variability in stroke lesions and language system reorganization. So far, our knowledge is limited about how to apply tDCS in a damaged network as in the case of aphasia. Therefore, with our present understanding of tDCS in aphasia, clinical application in the sub-acute phase is not yet recommended. Before applying tDCS in a clinical setting, future research is needed to improve our understanding of aphasia recovery on a neural level and how we can use this information to optimize timing of tDCS treatment and tDCS electrode configurations.

FUTURE PERSPECTIVES

The results of this thesis imply that clinical application of tDCS in sub-acute aphasia is not yet recommended. Future studies need to focus on 1) improving our understanding of neural recovery after stroke, 2) improving conventional non-invasive neurostimulation techniques, and 3) improving the application of non-invasive neurostimulation techniques in individual stroke patients.

Studying neurophysiological changes in aphasia recovery may give insights in the optimal timing of tDCS to support neuroplasticity. Cellular and molecular events related to stroke recovery have so far been based on animal studies, but whether and how this can be translated to humans is currently unclear.[49] The optimal timing of aphasia treatment, but also successful application of techniques like tDCS depend on our understanding of these processes. Brain structure and function, recently discussed as an important biomarker in stroke rehabilitation,[50] can be studied with neuroimaging techniques.

Interestingly, the ongoing PLORAS study (Predicting Language Outcome and Recovery After Stroke) aims to predict aphasia recovery in relation to lesion characteristics,[51] and will be of importance for our understanding of language system reorganization after stroke. Future results of this study may provide information on crucial areas for aphasia recovery, which may provide insights in potential target areas to develop individualized tDCS treatment. Whereas the PLORAS study gathers structural lesion scans, as suggested in chapter 7, it will be of importance to better understand how different areas are connected with each other. Advanced neuroimaging techniques such as Functional Connectivity Analysis (FCA)[52] or structural Diffusion Tensor Imaging (DTI) are useful network approaches.

Future studies may improve the conventional tDCS technique, such as the spatial and temporal characteristics. High Definition (HD-) tDCS is already a more advanced technique compared to conventional tDCS; electrodes are smaller and therefore this improves the focality.[53] Another recent consideration is the timing of tDCS and whether we should take into account the present brain state. Transcranial Alternating Current Stimulation (tACS), is an upcoming technique which may overcome this issue by interacting with ongoing cortical activity.[54] These developments may improve the precision of tDCS when targeting specific brain areas. Another recent development is network-targeted tDCS; one study with healthy subjects showed that an 8-electrode montage, compared to the conventional 2-electrode montage, enhanced tDCS effects in the targeted area and its' associated resting state network.[55] These new techniques, HD-tDCS, tACS and network-targeted tDCS, and its' underlying mechanisms have so far mostly been studied in motor functioning. For the application of these techniques in aphasia rehabilitation, it will also be important to study whether we can generalize the findings for motor functioning to language functioning.[56, 57] As also proposed in chapter 5, cerebellar tDCS effects on cortical motor areas have been studied, whereas these effects remain to be studied specifically for cortical language areas. In the case of language functioning, techniques such as electroencephalography (EEG) may be used to explore tDCS effects on ongoing activity in areas of the cortex associated with language.

Finally, it will be important for these technological developments to take into account the effects in a stroke population. Computer models are useful to study the influence of the lesion on the current flow of tDCS.[58] One study has studied this specifically with aphasic patients and has found that when taking into account a lesion, the electrodes may be placed differently per individual to realize optimal stimulation of a target area.[59] Finally, the population of people with post-stroke aphasia is heterogeneous, with a variety in stroke lesions, and with regards to the language impairment there is variety in severity and in the underlying language deficits. To understand the application of

tDCS in aphasia, future studies need to identify patient characteristics in relation to tDCS effects,[9] such as aphasia severity.[60] This enables the identification of patients who are responsive to tDCS, which may help to direct future tDCS interventions.

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Summary

The introductory **chapter 1** describes the background of this thesis. The concept of neuroplasticity is introduced, and the distinction between spontaneous neuroplasticity and treatment-induced neuroplasticity is described. The potential of non-invasive brain stimulation techniques to modulate neuroplasticity in aphasia recovery is discussed. Specifically, there is an interest in transcranial Direct Current Stimulation (tDCS) in clinical neurorehabilitation, because this technique is user-friendly and has limited side-effects. This thesis aims to improve our understanding of neuroplasticity in post-stroke aphasia, and explores whether neuroplasticity can be promoted with tDCS to enhance aphasia treatment effects.

Chapter 2 presents the study protocol of a double-blind randomized controlled trial (RCT) to investigate the effect of tDCS in post-stroke sub-acute aphasia. This multi-center RCT was designed to investigate whether tDCS enhances the effect of aphasia treatment in the sub-acute phase post-stroke. In the context of a regular rehabilitation program, patients with aphasia participated in two intensive, separate treatment weeks in which word-finding therapy was combined with either active tDCS or sham-tDCS over the left inferior frontal gyrus (left-IFG). The primary outcome measure was the Boston Naming Test (BNT), which was administered at baseline, directly after both intervention weeks and at 6 months follow-up. Other outcome measures included performance on trained and untrained picture items in each intervention week, and tests/questionnaires to assess verbal communication, participation and quality of life.

Chapter 3 describes the results of this RCT. Both the experimental (n=26) and control group (n=32) improved on the BNT, however, we found no significant differences between the groups over the intervention period or follow-up. For the other outcome measures, there were no significant differences between the groups either. Therefore, the results of this RCT do not support an effect of tDCS in post-stroke sub-acute aphasia.

In **chapter 4** we report on a within-subject design protocol to compare different electrode configurations of tDCS in patients with chronic aphasia. We describe language performance of 13 participants who took part in three single word-finding therapy sessions; in each session a different tDCS condition was applied. In the first session sham-tDCS was applied. In sessions 2 and 3 two different active tDCS configurations were used and counterbalanced across subjects: anodal tDCS was either applied over the left-IFG or over the left superior temporal gyrus (left-STG). Naming performance on trained and untrained picture items were used as outcome measures. Results reveal that, on a group level, participants improve more on trained items during the active left-IFG condition. On an individual level it was possible for some, but not all participants, to choose an optimal configuration, based on a pre-set criterion for proportional improvement in a

single therapy session. For these participants, the left-IFG condition lead to a larger post-treatment increase in naming trained items, compared to the other two conditions. Only the performance on trained items could be used as a guidance to choose an optimal configuration due to the lack of improvement on untrained items after single sessions.

In **chapter 5** we studied the effect of cathodal tDCS applied over the right cerebellum in healthy participants. We aimed to replicate the results of a between-subject study by Pope and Miall (2012) who found that cathodal tDCS over the right cerebellum in healthy participants enhanced the verbal reaction time on a verb generation task. We performed a within-subject design with two visits. During each visit, participants had to perform a verb generation task before and after tDCS; sham or cathodal tDCS was counterbalanced across the two visits. Results reveal that there was no effect of tDCS immediately after stimulation, thus we did not replicate the results of Pope and Miall (2012). However, in our within-subject design, we found that the group receiving sham-tDCS in the first visit performed better in the second visit, compared to the group starting with cathodal tDCS in the first visit. This finding suggests a tDCS-induced negative consolidation effect such that the right cerebellum plays a role in verbal learning, and that inhibiting the right cerebellum may reduce the learning rate. Similar tDCS-induced negative consolidation effects have also been described in motor studies. Our results in **chapter 5** suggest that long term effects of cerebellar tDCS needs to be further explored, before undertaking clinical studies with post-stroke patients with aphasia.

A prospective cohort study is described in **chapter 6,** in which we investigated the role of the Val66Met BDNF polymorphism in the recovery from aphasia. In animal studies and motor studies in healthy humans, carriers of this polymorphism showed less learning capacities than non-carriers. We investigated whether carriers of the polymorphism show less improvement on two language tests during their inpatient stroke rehabilitation program, compared to non-carriers. Language test performance was assessed at admission and discharge from the inpatient rehabilitation program, and the improvements on two language tests were used as outcome measures. Results revealed no significant differences in improvement between the two groups and therefore this study does not support the hypothesis that carriers of the polymorphism have a less favorable aphasia treatment outcome.

Chapter 7 presents a neuroimaging study of three patients with post-stroke chronic non-fluent aphasia. This study aimed to explore maladaptive plasticity in persistent verb anomia; brain activation maps associated with naming errors (i.e. semantic paraphasia) occurring in an oral verb picture-naming task were identified with an event-related fMRI paradigm. These maps were compared with those obtained in a previous study examin-

ing adaptive plasticity (i.e. successful verb naming) in the same participants. The activation patterns related to naming errors and successful naming show overlap in a number of common areas, suggesting that these areas contribute both to maladaptive and adaptive neuroplasticity processes. Therefore, the segregation of brain areas provides only a partial view of the neural basis of verb anomia and successful verb naming. As such, it indicates the importance of network approaches which may better capture the complexity of maladaptive and adaptive neuroplasticity processes in anomia recovery.

In **chapter 8**, the main findings of this thesis are recapitulated and discussed. Further, methodological considerations, clinical implications and future perspectives are described.

Samenvatting

Hoofdstuk 1 is een algemene inleiding van dit proefschrift. De term neuroplasticiteit wordt geïntroduceerd en de begrippen spontane en therapie-geïnduceerde neuroplasticiteit worden besproken. Een recente ontwikkeling in de klinische neurorevalidatie is de toepassing van niet-invasieve neurostimulatie technieken bij de behandeling van afasie; deze technieken kunnen neuroplasticiteitsprocessen beïnvloeden. *Transcraniële Direct Current Stimulatie* (tDCS) is een populaire neurostimulatie techniek, omdat het gebruiksvriendelijk is en weinig bijwerkingen heeft. Dit proefschrift gaat over neuroplasticiteit bij afasie ten gevolge van een beroerte, en heeft als doel om te onderzoeken of neuroplasticiteit kan worden beïnvloed met tDCS om de effecten van afasietherapie te vergroten.

Hoofdstuk 2 beschrijft een studieprotocol van een geblindeerde, gerandomiseerde studie dat is opgezet om de effectiviteit te onderzoeken van tDCS, bij mensen met afasie in de vroege fase na een beroerte. Het doel van deze studie, waarin is samengewerkt met meerdere revalidatiecentra, is om te onderzoeken of de toepassing van tDCS het effect van vroege afasietherapie kan vergroten. Participanten kregen twee aparte intensieve interventieweken waarbij de reguliere afasietherapie werd vervangen door woordvindingstherapie gecombineerd met actieve tDCS (experimentele groep) of sham-tDCS (controlegroep; pseudo-stimulatie) over de linker inferieure frontale gyrus (IFG). De primaire uitkomstmaat was de Boston benoemtest (BBT); deze test werd afgenomen voor en na elke interventieweek, en op zes maanden na de interventie. Andere uitkomstmaten waren de benoemscores op getrainde en ongetrainde plaatjes na elke interventieweek, en testen/vragenlijsten voor de verbale communicatie, participatie en kwaliteit van leven.

In **hoofdstuk 3** worden de resultaten beschreven van de geblindeerde, gerandomiseerde studie die is beschreven in hoofdstuk 2. Zowel de experimentele groep (n=26) als de controlegroep (n=32) gingen vooruit op de BBT, er waren echter geen significante verschillen in verbetering over de interventieperiode of over de zes maanden periode na de interventie. Er waren ook geen significante verschillen gevonden tussen de groepen op de andere uitkomstmaten. De resultaten in hoofdstuk 3 tonen aan dat er geen bewijs is dat tDCS het effect van vroege afasietherapie kan vergroten.

In **hoofdstuk 4** wordt een protocol geëvalueerd om verschillende tDCS elektroden configuraties te vergelijken bij mensen met chronische afasie na een beroerte. Dertien mensen hebben meegedaan aan drie sessies woordvindingstherapie; elke sessie werd gecombineerd met een verschillende tDCS conditie. In de eerste sessie werd therapie gecombineerd met sham-tDCS (pseudo-stimulatie). In sessies 2 en 3 werd therapie gecombineerd met actieve tDCS: anodale tDCS werd geplaatst over de linker IFG of

over de linker superieure temporale gyrus (STG). Als uitkomstmaat hebben we gekeken naar het benoemen van getrainde en ongetrainde plaatjes. Vervolgens wilden we ook per persoon een optimale tDCS conditie bepalen aan de hand van vooraf opgestelde criteria voor verbetering. De resultaten van de gehele groep laten zien dat mensen meer verbeterden op het benoemen van getrainde plaatjes tijdens de actieve IFG conditie in vergelijking met de twee andere condities. Op individueel niveau hebben we gevonden dat het voor sommige deelnemers mogelijk was om een optimale tDCS conditie te kunnen bepalen; voor deze subgroep ging het benoemen van getrainde plaatjes beter tijdens de actieve IFG conditie. Alleen het benoemen op de getrainde plaatjes kon gebruikt worden om een optimale tDCS conditie te bepalen; er was namelijk geen verbetering in het benoemen van ongetrainde plaatjes na de sessies.

In **hoofdstuk 5** hebben we het effect onderzocht van cathodale tDCS over het rechter cerebellum bij gezonde deelnemers. Het doel van deze studie is om de resultaten te repliceren van een eerdere studie. Deze eerdere studie, die gebruik maakte van een *between-subject design*, vond dat cathodale tDCS over het rechter cerebellum bij gezonde deelnemers leidde tot een verbetering van de reactietijd op een *verb generation* taak. Op een *verb generation* taak moeten deelnemers een werkwoord noemen bij een gegeven zelfstandig naamwoord, dus bijvoorbeeld bij het woord 'pen' moet de deelnemer 'schrijven' zeggen. Wij hebben een *within-subject design* studie opgezet waarbij elke deelnemer naar twee bezoeken moest komen; tijdens elk bezoek moesten ze zowel voor als na tDCS een *verb generation* taak doen. De volgorde van cathodale tDCS of sham-tDCS (pseudo-stimulatie) over het rechter cerebellum, werd *gecounterbalanced* over de twee bezoeken. Resultaten tonen aan dat er geen toegevoegd effect was van cathodale tDCS direct na stimulatie, daarmee hebben we dus niet de resultaten van de eerdere studie gerepliceerd. Echter, de groep die tijdens het eerste bezoek sham-tDCS kreeg deed het tijdens het tweede bezoek beter dan de groep die begon met cathodale tDCS tijdens het eerste bezoek. Dit resultaat suggereert een zogenaamde negatieve consolidatie-effect; het rechter cerebellum zou een rol spelen bij leren en het remmen van het rechter cerebellum zorgt voor een negatief effect op het leerproces. Dit tDCS-geïnduceerde negatieve consolidatie-effect is ook beschreven in motorische studies. Onze resultaten in hoofdstuk 5 suggereren dat bij de toepassing van tDCS over het cerebellum verder onderzoek nodig is naar lange termijn effecten voordat we zouden kunnen overgaan naar een toepassing van cerebellaire tDCS bij mensen met afasie.

In **hoofdstuk 6** wordt een prospectieve cohort studie beschreven waarbij de rol van het Val66Met BDNF polymorfisme op het herstel van afasie is onderzocht. Op basis van dierstudies en motorische studies met gezonde mensen, is gevonden dat dragers met het polymorfisme minder leercapaciteiten hebben dan niet-dragers. Het doel van de

studie in hoofdstuk 6 is om te onderzoeken of dragers, in vergelijking tot niet-dragers, minder vooruit gaan op twee taaltesten na een klinisch revalidatieprogramma. De twee taaltesten zijn afgenomen bij het startmoment en het ontslagmoment van de klinische revalidatie. De verbetering op deze twee taaltesten hebben we vergeleken tussen dragers en niet-dragers. Resultaten tonen aan dat er geen significante verschillen waren in de vooruitgang op de taaltesten tussen dragers en niet-dragers; onze resultaten ondersteunen dus niet de hypothese dat dragers een minder gunstige afasietherapie uitkomst hebben.

In **hoofdstuk 7** beschrijven we een functionele *neuroimaging* studie bij drie mensen met chronische niet-vloeiende afasie. Het doel van deze studie is om de hersengebieden in kaart te brengen die betrokken zijn tijdens het incorrect benoemen van afbeeldingen, dit is dus gerelateerd aan 'maladaptieve' neuroplasticiteit. Per individu zijn activatiemappen gemaakt op basis van een *neuroimaging* taak waarbij de deelnemers afbeeldingen moesten benoemen; bij elke afbeelding moesten zij het passende werkwoord noemen. Deze individuele activatiemappen hebben we vergeleken met een eerdere studie waarbij we in dezelfde mensen hebben gekeken naar de hersengebieden die betrokken zijn tijdens het correct benoemen van afbeeldingen (dit is dus gerelateerd aan 'adaptieve' neuroplasticiteit). Resultaten laten zien dat bepaalde hersengebieden zowel actief zijn tijdens incorrect benoemen als tijdens correct benoemen. Het segregeren van hersengebieden geeft dus maar gedeeltelijk informatie over de neurale basis van incorrect en correct benoemen. Een netwerkbenadering zal mogelijk beter de complexiteit van maladaptieve en adaptieve neuroplasticiteitsprocessen in kaart kunnen brengen.

Hoofdstuk 8 is de algemene discussie van dit proefschrift. De belangrijkste bevindingen worden beschreven en bediscussieerd. Sterke en zwakke punten van de onderzoeken worden beschreven. Ten slotte worden implicaties voor de klinische praktijk en aanbevelingen voor toekomstig onderzoek besproken.

Dankwoord

En dan is bijna het einde in zicht…Nu alle andere hoofdstukken zijn geschreven, mag ik beginnen aan het laatste onderdeel van dit boekje: het dankwoord. Ik wil een ieder bedanken die op enige wijze betrokken is geweest bij de totstandkoming en het schrijven van dit proefschrift. Een aantal mensen wil ik in het bijzonder bedanken:

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About the author

CURRICULUM VITAE

Kerstin Spielmann was born in Rotterdam on the 13th of May 1990. She attended secondary school at Johannes Calvijn (VWO) in Barendrecht, where she graduated in 2008. In the same year she started her study Psychology at the Erasmus University in Rotterdam. In 2011 she obtained her Bachelor's degree. She continued with a Master of Science in Neuropsychology at the University of Maastricht and finished her Master thesis at the Université de Montréal in Montréal, Canada. She obtained her Master degree Cum Laude in 2013 and in the same year she started working on the research described in this thesis at the department of Rehabilitation Medicine of the Erasmus MC, as part of the research group Rotterdam Neurorehabilitation Research (RoNeRes). Next to her research, she gained experience in neuropsychological diagnostics within the aphasia rehabilitation team of the Rijndam rehabilitation institute and diagnosed patients with acquired brain injury. She was also temporarily active as a teacher for first year Psychology students at the Erasmus University. At present she works as a neuropsychologist at Bartiméus, a low vision rehabilitation institute, and treats patients with visual impairments after acquired brain injury.

LIST OF PUBLICATIONS

Spielmann K, Durand E, Marcotte K, Ansaldo AI. Maladaptive Plasticity in Aphasia: Brain Activation Maps Underlying Verb Retrieval Errors. *Neural Plasticity. 2016; 4806492. Epub 2016 Jun 27.*

Spielmann K, van de Sandt-Koenderman WME, Heijenbrok-Kal MH, Ribbers GM. Transcranial direct current stimulation in post-stroke sub-acute aphasia: study protocol for a randomized controlled trial. *Trials. 2016 Aug 2;17:380*

Spielmann K, van der Vliet R, van de Sandt-Koenderman WME, Frens MA, Ribbers GM, Selles RW, van Vugt S, van der Geest JN, Holland P. Cerebellar Cathodal Transcranial Direct Current Stimulation and Performance on a Verb Generation Task: A Replication Study. *Neural Plasticity. 2017:1254615. Epub 2017 Feb 14.*

de Boer RGA, **Spielmann K**, Heijenbrok-Kal MH, van der Vliet R, Ribbers GM, van de Sandt-Koenderman WME. The Role of the BDNF Val66Met Polymorphism in Recovery of Aphasia After Stroke. *Neurorehabilitation and Neural Repair. 2017 Sep;31(9):851-857.*

Spielmann K, van de Sandt-Koenderman WME, Heijenbrok-Kal MH, Ribbers GM. Evaluation of a protocol to compare two configurations of Transcranial Direct Current stimulation for aphasia treatment. *Journal of Rehabilitation Medicine. [in press]*

Spielmann K, van de Sandt-Koenderman WME, Heijenbrok-Kal MH, Ribbers GM. Transcranial Direct Current Stimulation does not improve language outcome in sub-acute post-stroke aphasia. *Stroke. [in press]*

Blom-Smink M, **Spielmann K,** Mendez Orellana CP, Ribbers GM, Crinion J, Smits M, van de Sandt-Koenderman WME. The Neural Correlates of Anomia Therapy in Subacute Post-stroke Aphasia: Language Lateralization and the Influence of Lesion Volume and Lesion Site. *[Submitted]*

SUMMARY OF PhD TRAINING AND TEACHING ACTIVITIES

Name PhD student:	**Kerstin Spielmann**	**PhD period:**	**2013-2017**
Erasmus MC Department:	Rehabilitation Medicine	**Promotor:**	Prof. dr. G.M. Ribbers
Research School:	Netherlands Institute for Health Sciences (NIHES)	**Supervisor:**	dr. W.M.E. van de Sandt

1. PhD training

	Year	Workload
General academic skills		
• Endnote (Medical Library)	2014	3 hours
• Pubmed (Medical Library)	2014	3 hours
• Literature search (Medical Library)	2014	3 hours
• BROK course (Basiscursus Regelgeving Klinisch Onderzoek)	2015	30 hours
• CPO course	2015	7 hours
Research skills		
• Advanced topics in clinical trials (NIHES)	2015	35 hours
• English Biomedical Writing and Communication	2015	25 hours
• Biostatistics for clinicians (NIHES)	2015	25 hours
• Health economics (NIHES)	2015	15 hours
• Health services research (NIHES)	2015	15 hours
• Science Integrity	2016	7 hours
• Missing data analysis, University of Amsterdam, Amsterdam	2015	4 hours
In depth courses		
• fMRI/SPM course, Utrecht	2013	24 hours
• fMRI safety course	2014	5 hours
Seminars and workshops		
• FESN summer school 'From Clinic to Research: Designs, Analyses, Ethics', Berlin	2014	33 hours
• Cognitive Rehabilitation training, ACRM conference, Toronto	2014	16 hours
• CATS training school: International Classification of Functioning, Disability and Health as it applies to aphasia research, H' Attar, Malta	2015	24 hours
• Aphasia Clinics: technical advances, Rotterdam	2015	6 hours
Oral presentations		
• 'Transcranial Direct Current Stimulation in sub-acute aphasia', regional meeting for rehabilitation physicians, Rotterdam	2014	10 hours
• 'Transcranial Direct Current Stimulation in sub-acute aphasia', work group tDCS, Rotterdam	2014	10 hours

• 'Transcranial Direct Current Stimulation in sub-acute aphasia', workgroup 'CVA Nederland', Apeldoorn	2014	10 hours
• 'Transcranial Direct Current Stimulation in sub-acute aphasia', department of Radiology, Erasmus MC, Rotterdam	2014	10 hours
• 'Transcranial Direct Current Stimulation in sub-acute aphasia', Aphasia Junior Days, Groningen	2014	12 hours
• 'Transcranial Direct Current Stimulation in sub-acute aphasia', Afasienet conference, Zeist	2015	10 hours
• Symposium 'Transcranial Direct Current Stimulation to treat aphasia', IBIA conference, Den Haag	2016	20 hours
• 'Transcranial Direct Current Stimulation to treat aphasia', Neuro and Rehabilitation conference, Utrecht	2016	12 hours
• 'Transcranial Direct Current Stimulation in sub-acute aphasia', Aphasia Junior Days, Groningen	2016	12 hours
• Symposium 'Transcranial Direct Current Stimulation to treat aphasia', IBIA conference, New Orleans	2017	20 hours
• 'Transcranial Direct Current Stimulation to treat sub-acute aphasia: results from an RCT', workgroup rehabilitation, University Medical Center Utrecht, Utrecht	2017	12 hours
• 'Transcranial Direct Current Stimulation to treat sub-acute aphasia: results from an RCT', Afasienet conference, Zeist	2017	12 hours
• 'Transcranial Direct Current Stimulation to treat sub-acute aphasia: results from an RCT', DCRM conference, Maastricht	2017	12 hours

Poster presentations

• 'Transcranial Direct Current Stimulation (tDCS) to enhance treatment effects in aphasia', ACRM conference, Toronto	2014	8 hours
• 'Applying Transcranial Direct Current Stimulation (tDCS) in a clinical setting: a pilot study', NNR conference, Maastricht	2015	8 hours
• 'Applying Transcranial Direct Current Stimulation (tDCS) in a clinical setting: a pilot study', Science of Aphasia conference, Aveiro	2015	8 hours
• 'Transcranial direct current stimulation in neurorehabilitation', Rotterdam Stroke Services, Rotterdam	2015	5 hours
• 'The additional effect of Transcranial Direct Current Stimulation (tDCS) in post stroke sub-acute aphasia: a pilot study', IBIA conference, Den Haag	2016	5 hours
• 'The additional effect of Transcranial Direct Current Stimulation (tDCS) in post stroke sub-acute aphasia: a pilot study', Neurocontrol symposium, Egmond aan zee	2016	5 hours
• 'Comparing two electrode configurations of Transcranial Direct Current Stimulation (tDCS) in post-stroke chronic aphasia', CATS symposium, Rotterdam	2017	8 hours
• 'The effect of cerebellar transcranial direct current stimulation (c-tDCS) on language task performance: a replication study', Brain Stimulation conference, Barcelona	2017	8 hours
• 'Comparing two electrode configurations of Transcranial Direct Current Stimulation (tDCS) in post-stroke chronic aphasia', NNR conference, Maastricht	2017	8 hours

(Inter)national conferences

• American Conference of Rehabilitation Medicine (ACRM), Toronto, Canada	2014	24 hours
• Dutch Conference of Rehabilitation Medicine (DCRM), Rotterdam, The Netherlands	2014	16 hours
• International Aphasia Rehabilitation Conference (IARC), Den Haag, The Netherlands	2015	24 hours
• Neurorehabilitation and Neural Repair (NNR), Maastricht, The Netherlands	2015	16 hours
• Science of Aphasia (SOA) Conference, Aveiro, Portugal	2015	16 hours
• International Brain Injury Association (IBIA), Den Haag, The Netherlands	2016	16 hours
• Neurobiology of Language conference, London, The United Kingdom	2016	16 hours
• Collaboration of Aphasia Trialists (CATs), Rotterdam, The Netherlands	2017	16 hours
• Brain Stimulation conference, Barcelona, Spain	2017	24 hours
• International Brain Injury Association (IBIA), New Orleans, USA	2017	16 hours
• Neurorehabilitation and Neural Repair (NNR), Maastricht, The Netherlands	2017	16 hours

Other

• Participating in research meetings, department of Rehabilitation Medicine, Rotterdam	2013-2017	160 hours
• Organizing and participating in RoNeRes meetings, department of Rotterdam Neurorehabilitation Research	2013-2017	28 hours
• Co-editor Medigrip, an application for rehabilitation physicians	2015-2016	30 hours

2. Teaching activities

Other

• Supervising master thesis (systematic review), student Linguistics	2015	16 hours
• Supervising master thesis, student Neuropsychology	2015	16 hours
• Supervising bachelor thesis, 2 students Speech and Language Therapists in training	2016	20 hours