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TRANSCRANIAL DIRECT CURRENT STIMULATION AS A TOOL TO INDUCE LANGUAGE RECOVERY IN PATIENTS WITH POST-STROKE APHASIA: AN OVERVIEW OF STUDIES

In recent years, possible therapeutic effects of transcranial direct current stimulation (tDCS) have been widely investigated in studies of different types of neural pathologies. Recent reviews of tDCS in patients with post-stroke aphasia did not provide coherent evidence oa its efficiency. There were no uniform protocols of stimulation, patient selection criteria were highly divergent, and the reports of treatment outcomes varied dramatically. In this review, we focus on the reported heterogeneity of tDCS effects trying to disentangle its putative underpinnings rooted in the diversity of lesion types, aphasia severity and recovery stages. Given the current theoretical models suggesting qualitatively different patterns of brain activity which accompany aphasia recovery, various physiological factors should be taken into account to choose optimal tDCS parameters. With this in mind, we assess the results of ten studies applying tDCS in post-stroke aphasia treatment, and suggest directions for further research in this rapidly developing field.

Keywords: aphasia, tDCS, non-invasive brain stimulation, neuroplasticity, neurorehabilitation, stroke.

JEL Classification: Z

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Introduction

Electrical currents were first used for treatment in clinical medicine more than two centuries ago (Priori, 2003). However, experimental evidence of the impact of electrical currents on brain excitability was obtained only in the 20th century. For example, a study by Bindman et al., 1964), showed that small electrical currents delivered through intracerebral or epidural electrodes for 2-10 minutes could induce sustainable cortical activity in rat brain lasting 1-5 hours after the stimulation. Further studies, which applied direct current non-invasively in humans (Nias, 1976; Rush et al, 1968) showed that such a method of stimulation, called transcranial direct current stimulation (tDCS), can lead to physiological and functional effects, both in healthy participants and in patients. More recently, the tDCS technique has been applied for modulation of cortical activity in humans - in a range of experimental and clinical situations (Lefaucheur et al., 2017). This method has become widely used for modulating cognitive functions in normal conditions and for facilitating recovery in various clinical groups, including patients with post-stroke aphasia (Shah et al., 2013; Monti et al., 2014; Elsner et al., 2016).

The tDCS procedure is carried out with a battery-driven device. A range of manufacturers produce devices with a variable degree of customisation of the stimulation parameters (such as current intensity, shape, duration, or even complex patterns of current). Most typically, two saline-soaked electrodes plugged into this device are used for delivering the electrical current to the scalp surface. The active electrode, which can be either anodal or cathodal, is placed on the scalp. The other electrode, a reference, may be placed either away from the head or on the supraorbital region (Nitsche et. al, 2008); sometimes, both anodal and cathodal electrodes are placed on the scalp for stimulating two foci, although this procedure is going out of practice. The size of the electrodes varies: e.g. 5x5 cm, 5x7cm and other. The current intensity is typically 1-2 mA, and the duration of stimulation rarely exceeds 30 minutes. According to the reviews of studies performed either with healthy participants or with patients (Brunoni et al., 2011; Poreisz et al., 2007), tDCS does not have any severe adverse effects. Subjects mostly report such feelings as tingling, itching, sometimes a headache, pain or a burning sensation during the stimulation procedure. However, all of the adverse effects recorded are short-term.

Physiological effects of tDCS are quite variable and are observed on different levels of the neural functioning: from a neurochemical level to large-scale connectivity (Hunter et al., 2013). The exact mechanisms of tDCS application at the neural level are still under discussion. In comparison with, for example, transcranial magnetic stimulation (TMS) (Pascual-Leone et al., 1998), which is

supposed to influence action potential generation in large neuronal populations, tDCS acts in a different way. As the current delivered by tDCS is weak, it does not cause any action potential generation per se. Nevertheless, it is sufficient to elicit a small and graded change in the resting neural potential (Neitsche et al., 2000). This way, tDCS application leads to a shift in the resting potential towards depolarization or hyperpolarization, making it more or less prone to excitation rather than causing the excitation per se. Hence, tDCS effect is considered as neuro*modulatory*. Critically, depending on the type of the active electrode, it is believed, based on the available experimental evidence, to modulate the neural activity in two different ways. Namely, anodal tDCS is considered an intervention which increases cortical excitability, whilst cathodal tDCS is considered an inhibitory one (Nitsche et al., 2000), although the exact electrophysiological underpinnings of this dichotomy are still under discussion. Notably, these differences in the effects of tDCS polarity have, for the most part, been observed in studies of the motor cortex. Hence, it does not necessarily mean that inhibitory or facilitatory effects of the particular stimulation polarity (cathodal/anodal) will be the same when tDCS is applied over other brain areas.

If the stimulation lasts just a few seconds, it causes only short-living online changes of cortical excitability (Nitsche et al., 2000) which become extinct as soon as the stimulator is turned off. If, however, the stimulation is applied for several minutes, it might cause changes that last beyond the stimulation period: up to one hour or even more (Nitsche et al., 2001), (Priori, 2003). The key role in the long-lasting effects of tDCS is attributed to long-term potentiation and long-term depression mechanisms. These mechanisms are driven by N-methyl D-aspartate (NMDA) receptors of the glutamatergic neurons. It was indeed shown that blockade of NMDA receptors reduces the effect of tDCS application (Liebetanz et al., 2002; Nitsche et al., 2003).

One of the most important parameters of tDCS procedure is the intensity of the stimulation sessions. There are results confirming that the repetition of simulation sessions enhances the effects provided by the application of direct currents on the cortex (Monte-Silva et al., 2013). However, according to the results of recent research (Batsikadze et al., 2013), the cumulative effect of repetitive tDCS stimulation is not universal: not in every subject an increase in intensity of stimulation caused an increase in its efficiency. This might be explained by the so-called ‘ceiling effect’, which can probably be observed in patients as well.

Notably, the physiological effects of tDCS can be observed widely across the brain: it has been shown (for a review see Hunter et al., 2013) that tDCS affects not only the stimulated area, but also distant cortical regions. A possible reason for this is that such regions may be structurally and

functionally connected with the stimulated area forming a common neural network (Venkatakrishnan et al., 2012). This, of course, does not exclude the possibility that some of such distant effects may stem from the physical properties of head tissues (include the various skin, skull and brain tissues) as electrical conductors, directing the current to areas other than the stimulation site.

The effects of tDCS described above are usually more generally considered as neuroplastic processes. Neuroplasticity is an "umbrella" term covering a variety of sustainable changes occurring in the brain on different functional levels that are caused by various internal and external factors such as salient environmental events, behavioural experience, brain injury, diseases (Johansen-Berg, 2016). Neuroplasticity is a crucial ability of the brain to change its structural and functional properties throughout time adjusting itself to either normal or pathological conditions. tDCS is believed to be capable of inducing synaptic plasticity through long-term potentiation and long-term depression mechanisms (Liebetanz et al., 2002). Neural diseases lead to specific and long-lasting changes in the brain function, hence tDCS may have therapeutic potential for treating brain dysfunctions by facilitating recovery-related plastic changes. In this paper, we focus on the efficiency of tDCS application in post-stroke aphasia rehabilitation.

Application of tDCS in post-stroke aphasia

Aphasia is a disorder common for patients with a left-hemispheric stroke (Ardila, 2014). This disorder is among the most important and debilitating consequences of stroke. Depending on the lesion location, aphasic patients can have difficulties in language production, language comprehension or both. The severity of these dysfunctions can also differ. Typical production or/and comprehension dysfunctions in aphasic patients usually demonstrate dynamics across three stages following a stroke. The acute stage begins just after the stroke and lasts for about two weeks. The sub-acute stage follows the acute stage and lasts up to 4 months after the stroke. The chronic stage begins after the sub-acute stage if a complete recovery is not reached by that time. The goal of tDCS for aphasia is to change the activation patterns of language networks to make it more functional – probably by inducing plastic processes that promote language recovery (Shah, 2013, Lefaucheur, 2017).

Several meta-analyses of tDCS application in post-stroke aphasia have been published in recent years (Monti et al., 2013; Shah et al., 2013; Elsner et al., 2013; Lefaucheur et al., 2017). In brief, the results of the studies reviewed by these papers do not allow reliable conclusions about the

effectiveness of tDCS in aphasia to be made. There are in general few studies on this issue (the largest number is 21 studies in the review by Monti et al., 2013) and the evidence of therapeutic effects of tDCS provided in them is insufficient.

Beyond such an obvious limitation as the small sample sizes, the inconsistency of results was related to heterogeneous designs (parallel or cross-over design, sham-controlled and uncontrolled etc.), the variability of tDCS protocols (anodal, cathodal, combined stimulation of different sites and hemispheres, different current strength and stimulation duration) and patient demographic and clinical characteristics (age, education, term post-stroke, aphasia type and severity, lesion site etc.) (Elsner et al., 2013). It is highly possible that these methodological parameters might impact the possible therapeutic effectiveness of tDCS (Monti et al., 2013). The main conclusion of these reviews is for future studies to focus on improving experimental designs, finding optimal stimulation and therapy parameters, and fine-tuning them on the basis of individual patient characteristics. These methodological improvements might help make assessments of tDCS more reliable.

Still, this is not the only point to address in future studies and reviews. Shah et al., 2013 note that present studies do not provide evidence for any relation between behavioural improvements and functional changes in the brain, putatively induced by tDCS. The ultimate goal of tDCS application is to change the patterns of activity of neural networks to improve the language functions at the behavioural level, i.e. in normal communication settings.

Some authors suggest that recovery is generally driven by the re-activation of the perilesional left-hemispheric neural networks (for review see (Hamilton et al., 2011; Anglade et al., 2014)). These authors put forward the idea that aphasic patients might have latent functional language resources in the left hemisphere. Stimulation is considered a means to activate these resources. In this case, anodal tDCS is applied over the perilesional left hemispheric areas, usually Broca's or Wernicke's area. The other approach, whilst not contradicting the previous one, focuses on the activity in the right-hemispheric language area homologues, which is commonly believed to be dysfunctional or counterproductive for recovery. Hence, some authors use cathodal tDCS to inhibit the brain activity in these regions. There is also a third approach which combines both the left-hemispheric facilitation and the right-hemispheric inhibition: several studies have used anodal tDCS over the left hemisphere and cathodal tDCS over the right hemisphere together in the same aphasic patients. In this latter case, tDCS application is expected to cause a leftward laterality shift in the language-related neural

activity, the goal being to normalize the functional hemispheric distribution of bilateral language networks.

The utility of these approaches to aphasia treatment may be better understood by referring to the rich experience of the application of non-invasive brain stimulation for patients with motor stroke. Motor stroke recovery is correlated with a reorganization of the bilateral cortical motor network (Grefkes et al., 2014). This reorganization occurs during three consecutive stages, similar to those discussed above for aphasia: acute, sub-acute and chronic. During the acute stage, movements of the paretic limb are accompanied by ipsilesional neural activation, which is abnormally weak. However, a few days later the motor-related brain activity becomes atypically strong and "bilateralizes", i.e. spreads over both hemispheres. With time, in the most successful recoveries, the activation balance shifts towards stronger neural activity in the ipsilesional hemisphere. In the most severe cases with incomplete recovery, the bilateral activation remains, and the contralesional hemisphere is suggested to play a compensatory role. A similar pattern of functional reorganization was also observed in the study of post-stroke aphasia recovery we reviewed above (Saur, 2006). In aphasia, abnormally weak activation in the acute stage is followed by bilateral overactivation of language areas in the sub-acute stage, with the recruitment of the right hemispheric areas. The latter has a compensatory role in the sub-acute phase, whilst in the chronic phase its role might be different; the right hemispheric involvement might be deleterious in mild-to-moderate cases, but in moderate-to-severe it could remain compensatory (Anglade et al., 2014). This similarity of reorganization patterns allows the authors to speculate that post-stroke aphasia recovery in each particular case depends on the functional contribution of activity within each hemisphere to language processing. The functional role of each hemisphere might be different depending on such individual parameters as lesion location, its functional severity and the recovery stage. Taking these parameters into account is important for studies using any kind of brain stimulation, including tDCS.

In our review we try to apply these ideas to the results of ten studies where tDCS was used to improve the language function in aphasia, mostly in the chronic stage. We pay attention to various factors, such as the location and functional severity of lesion, the recovery stages of patients included in the study samples. Such an analysis might be particularly helpful in the absence of neuroimaging data in these studies. The results of this analysis will help to suggest the probable impact of these factors on the interhemispheric activation balance, which, as discussed above, could be the main recovery factor. This approach might also help to explain the lack of consistent evidence of tDCS efficiency found in previous reviews. Such an analysis of individual patient characteristics

might help uncover variability of single patient outcomes, which can impact the averaged group effect. We first review studies where tDCS was applied over the left hemispheric language regions (according to the idea of its higher functional role in the recovery), and then several studies where tDCS was applied to the right hemisphere (according to the idea that its role in the recovery might be different depending on various factors).

Left-hemispheric tDCS in aphasia

In Fridriksson et al., 2011, eight chronic stroke patients with fluent aphasias underwent 10 computerized sessions of training in picture naming. These were combined with 20 minutes of tDCS given in two separate phases for each patient. Each phase lasted for one week with a three-week break between phases. In one phase, a 1 mA anodal tDCS was delivered over the left hemisphere, while in the other phase a sham tDCS protocol was used as a control. In both conditions (real and sham) an anodal electrode was placed over the left posterior perilesional areas, whilst the referent cathodal electrode was placed over the right forehead. The study was performed in a double-blind design: neither participants nor experimenter were aware about the stimulation condition used. Treatment outcome was measured using the patient performance in an object naming task for both trained and untrained words. The measurement was conducted six times for both conditions, including a follow-up three weeks later.

Statistical analysis of the response times was performed using 1-tailed Wilcoxon signed rank test after the exclusion of outliers. The results of the analysis made by the authors does not allow a reliable conclusion about tDCS effects on the response times in the object naming task to be made, even for the trained set of stimuli. The results of the statistical analysis for untrained stimuli are not presented in the paper.

There is a lack of information in the paper concerning the inclusion and exclusion criteria of patients. The authors only mentioned that all the participants had fluent aphasia of variable severity caused by posterior cortical and subcortical lesions; time post-stroke varied from 10 to 150 months; the sample consisted mostly of quite elderly participants. This variability may be considered a weak point of this study since aphasia is a disorder with a well-known high individual variability in language impairments, lesion-to-symptom mapping and recovery patterns (Ardilla, 2014). This also causes problems when analyzing the efficiency of the electrode placement selected in the study: the active electrode placement is not described properly and it does not correlate with the variability of aphasia types in the sample. As discussed above, patients with different severity of aphasia might

have different functional resources in the left hemisphere, so it is hard to establish the mechanisms underlying tDCS effects when such a small, heterogenous sample is analyzed. Overall, the inconsistencies in the design of the study do not allow to analyze properly the functional significance of the anodal tDCS application to the left posterior brain regions in this particular sample.

In Baker et al., 2010, an anodal tDCS was also applied to the left hemisphere, but in this case to its anterior part, i.e. over Broca's area. In contrast to the previous study, patient information is described in detail in this paper. The sample was heterogeneous, it included ten chronic aphasia patients either with Broca's or with anomic aphasia. The severity of aphasia and the locations and sizes of lesions were different. The term post-stroke varied across patients from 10 months to 20 years. The patients underwent treatment which combined a picture naming task with a 1-mA anodal tDCS delivered for 20 minutes per day over 5 consecutive days. A sham stimulation was delivered in the same design during a separate 5-day treatment session. The interval between the real and the sham session was 7 days. The order of sessions was randomized across subjects, which were also blinded to the stimulation type. However, the study was not double-blind as the experimenter manually switched off the device in the sham condition. Picture naming accuracy was used as the outcome measure taken just before, just after and one week after the therapy completion. It was assessed for both trained and untrained picture items.

Analysis performed using 2x2 repeated-measures ANOVA for naming the trained items showed a statistically significant effect of the stimulation type: more trained items were named correctly after anodal tDCS than after the sham condition. For the naming of untrained items, repeated-measures ANOVA also showed a statistical trend towards improvement after real tDCS as compared to the sham. In fact, only 3 out of 12 patients demonstrated a marked increase in the number of correctly named untrained pictures. All of these responders were characterized by post-stroke lesion localised within the left frontal lobe, whereas other patients had more posterior lesions. The authors concluded that anodal tDCS applied to the perilesional areas might be more beneficial and cause greater language improvements than attempts to stimulate speech cortical areas located far from the lesion.

Different problems arise if one considers the results obtained by Volpato et al., 2013. The main goal of their study was to find whether an off-line tDCS affects the recovery of the language function in any way. Offline tDCS is a protocol when stimulation is not combined with any kind of behavioural training, but is instead performed in a resting state only. In this study, although the patients did undergo a rehabilitation therapy, it was separated in time from the stimulation: it was delivered at

least 90 minutes before or after the stimulation session. The authors collected a sample of eight patients according to a clear set of criteria: premorbidly right-handed people, more than 6 months after a single left-hemispheric stroke, with mild-to-moderate aphasia and no other neurological disorders. However, patients were still quite different according to lesion locations, post-stroke terms and types of aphasia. Notably, all the patients in this sample had a mild-to-moderate aphasia severity. The stimulation procedure was performed in two sessions: one real stimulation session and one sham stimulation as a control. Each session took place over 5 consecutive days, with both sessions carried out within a period of two weeks. The order of sessions was counterbalanced across the patient group. The active anodal electrode was placed over Broca's area and a referent cathodal electrode was placed over contralateral supraorbital area. The blinding was done only for the person making outcome measures.

As an outcome measure, authors used a naming task, but in contrast with the previous studies, it included both object and action naming. The task was carried out three times: two weeks before the tDCS course, just before and just after it. A new list of items was used for every test to avoid repetition effects. Naming accuracy and response times were assessed.

Statistical analysis performed using ANOVA showed no differences either in accuracy or in response time between the real and sham conditions and between pre- and post-stimulation assessments. The authors found significant differences between response times in object and action naming tasks, which is typical for most of aphasics. As mentioned, the sample contained very different types of aphasia with different lesion locations. In this case, individual analysis becomes important. The descriptive analysis of individual responses revealed that only one of the patients sustainably improved both in accuracy and in response time. The authors note that this patient had the severest naming deficit before therapy and consequently, the largest difference between the pre- and post-intervention performance to show improvements. Still, usage of just a single outcome measure, a naming ability, for a sample of different aphasics does not allow a convincing analysis of individual outcomes. In the discussion, the authors suggest that one of the probable reasons for the lack of any effect is the off-line design itself. This might explain the absence of differences between the real and sham groups. As previously mentioned, tDCS-induced effects lasts for about an hour. In this particular case, it means that even if any effect was present during tDCS procedure, it did not interact with the effects of speech training, which started much later. Hence, the improvements made by several patients in the sample could be simply induced by training, and the results presented in the study do not allow an analysis of the tDCS efficiency per se.

One important aspect of variability in post-stroke aphasia is the particular recovery stage. As discussed above, the recovery is most intense at the sub-acute stage, and is almost over at the chronic stage. To address the potential of tDCS to assist recovery before the chronic stage sets in, a study by Polanowska et al., 2013, assessed patients with acute and sub-acute aphasia. The authors present clear inclusion and exclusion criteria. The sample is noticeably larger than in the studies reviewed above (N=24) and is quite homogeneous according to the type of aphasia – only non-fluent aphasics are included; it is still rather heterogeneous with respect to age, severity, lesion location and volume. Patients underwent tDCS over left frontal regions in two conditions: anodal or sham. Condition assignment was made by an independent investigator who used a computer randomization algorithm. Other investigators and participants were not aware of the condition used, providing a double-blind design. Two groups of patients with two conditions were counterbalanced according to demographical and clinical parameters. Each group received 15 consecutive sessions of speech-language therapy, combined with 10 minutes of anodal 1-mA tDCS over Broca's area in the real condition and 25 seconds of the same stimulation in the sham condition. To measure language improvements, a computerized picture naming testing was run before therapy, immediately after, and three months later. Naming accuracy and response times were assessed.

Patients in both the real and sham conditions showed improvement in naming accuracy immediately after the therapy course. However, no statistically significant differences in naming accuracy were found between the tDCS conditions, either just after the therapy or at the follow-up assessment. The response times improved (in terms of the effect size) in the real tDCS group only and were significant just after the therapy with a tendency in the follow-up measurement. No improvements in reaction times were observed in the sham group. However, the U-criteria did not show statistically significant differences between the real and sham groups either immediately after therapy or at the follow-up. The authors interpret their result as a weak evidence of the efficiency of anodal left-hemispheric tDCS for facilitating behavioural improvements in aphasic patients. As the sample was very heterogeneous, the authors tried to investigate the probable impact of different demographical and clinical parameters on the recovery. They consequently limited the sample to mild-to-moderate sub-acute patients without a large lesion. It is remarkable that this analysis revealed a tendency for a correlation with better improvements in the subgroup of patients with a post-stroke term of up to 90 days. This corresponds well with the account of the post-stroke aphasia language recovery reviewed above, which suggests that patients in the sub-acute stage have the highest recovery potential. The recovery at this stage is more correlated with the right-hemispheric overactivation (Saur et al.,

2006), rather than with the left-hemispheric underactivation. It can explain the weak tDCS-induced improvements of the potential best-responders group in comparison with the sham condition: possibly, an excitatory tDCS applied to the right hemisphere could have been more beneficial in this particular subgroup.

Such an approach of an accurate investigation of more homogeneous sub-groups of aphasic patients might be quite beneficial. Particularly interesting could be an investigation of the application of tDCS to different sites within one hemisphere. The tDCS studies discussed above only used an anodal stimulation applied either over anterior (inferior frontal) cortical areas or (in Fridriksson et al., 2011) the more posterior temporo-parietal language cortex. Further studies discussed below allow a more direct comparison between the effects of anodal vs. cathodal stimulation as well as those of anodal stimulation between anterior vs posterior stimulation sites.

In Marangolo et al., 2013, 12 patients with nonfluent aphasia underwent speech therapy combined with anodal tDCS applied consecutively to Broca's area and Wernike's area (and vice versa). Each of these montages was used for 5 consecutive days of a 2-week therapy course. A sham condition with a half the patient group, with the same two montages but with the stimulation time reduced to 30 seconds. The patients were selected according to clear inclusion criteria: right-handed left-hemispheric stroke patients at least 6 months after a stroke with no other severe neurological disorders. No exclusion criteria are presented in the paper. The authors also present MRI data which show that the maximal lesion overlap between the patient was localised in capsula externa, the claustrum and the putamen. The speech therapy for these patients included a 2-hour daily conversation with a speech therapist, during which video clips showing everyday situations were discussed. The other set of clips was presented before and after the treatment to assess the patients' speech production. For a 1-month follow-up, the same clips as used in the therapy session were used to test production. Speech complexity, sentence length and verbs used during video description were assessed. The authors hypothesised that application of anodal tDCS to Broca's rather than to Wernicke's area would lead to greater improvements in the quality and quantity of expressive speech.

Their statistical analysis supported this hypothesis: ANOVA showed greater improvements for the stimulation condition compare to the sham condition for such parameters as speech consistency and complexity. Further analysis showed significantly greater improvements for the Broca's condition comparing to the Wernicke's condition. ANOVA computed on the follow-up assessment results showed the persistence of these outcomes a month later.

This study demonstrates the effectiveness of accurate sample collection and optimal stimulation site selection. This is in line with the suggestion we made above that, given the high individual variability of aphasic patients, it is absolutely crucial to form homogeneous patients groups. Such an approach allows detectable and significant results to be obtained, as this study shows. Otherwise, in heterogeneous samples, any improvement effects in particular subgroups may be smeared or even cancelled out after averaging the outcomes across diverse patients. This approach also takes into account and demonstrates the functional heterogeneity of the stimulated areas and particularly supports the idea that perilesional areas are the most beneficial for the recovery process. The next study we review, however, provides a result that possibly contradicts this suggestion.

Monti et al., 2008 collected a sample of 8 chronic nonfluent aphasia patients. Unfortunately, the inclusion criteria are not fully presented in the article. The patients underwent a single tDCS session in one of the four conditions: anodal, cathodal and sham over the left fronto-temporal areas and a control condition over occipital cortex. The current intensity was 2 mA for all the conditions, the stimulation duration was 10 minutes for the real conditions and 10 seconds for the sham condition. Anodal and cathodal sessions were done in a random order with an interval of at least 1 week, implemented 2 months after the control condition session. A computerised picture naming task was used as an outcome measure, taken before and after each session. The naming accuracy and response times were assessed. The statistical analysis using two-way ANOVA showed no improvements in naming accuracy for the anodal and the sham group, but it showed improvements in the cathodal group. However, no significant improvements in response times were obtained in any of the stimulation groups. No significant effects were shown for the control condition either.

This controversial pattern of results could have a number of explanations; two factors appear most important. First, the patients underwent only a single tDCS session, whilst for reaching reliable excitatory or inhibitory effect of tDCS, most other studies have used repetitive stimulation sessions. A single application of tDCS, especially in a sample which might not be quite homogeneous, does not allow a reliable conclusion about the nature of physiological effect obtained.

Second, a precise inspection of the patients' individual results shows that the greatest improvements were demonstrated by three patients with global aphasia. It is known that global aphasia is a severe language disorder usually associated with a large lesion in the left hemisphere. In this case, the shift of language dominance to the right hemisphere is highly possible. Hence, the study suggests that the excitatory anodal stimulation of the right hemisphere might be beneficial in some cases.

To sum up, there is a lack of well-designed studies to make a reliable general conclusions of the efficacy of left-hemispheric tDCS in post-stroke aphasia. Most of the effects demonstrated are weak or, in some case, do not even reach statistical significance. However, the results of some studies (Marangolo et al, 2013; Polanowska et al, 2013) do suggest that anodal left-hemispheric tDCS over perilesional areas could be the most beneficial stimulation protocol, especially for mild-to-moderate patients in the chronic stage. This is in line with one hypothesis explaining bilateral language networks reorganization: the re-activation of the intact perilesional areas is the main factor driving the language recovery in transition from the sub-acute to the chronic stage.

Next we review studies, addressing the main alternative hypothesis, namely that of the deleterious role of the right hemisphere in aphasia recovery.

Right-hemispheric tDCS in aphasia

You et al. 2011 applied tDCS to a group of sub-acute aphasia patients in two conditions: anodal tDCS to the left STG or cathodal tDCS to the contralateral (right) STG. The sample consisted of 21 sub-acute patients with global aphasia caused by a single left-hemispheric ischemic stroke. In comparison with most of the studies reviewed above, this sample was more homogeneous with respect to such parameters as post-stroke onset, lesion location and volume. These patients underwent 10 sessions of speech therapy focused on naming, comprehension and increasing verbal output. Each session took 30 minutes and was combined with either real or sham stimulation. The real stimulation was delivered for 30 minutes with a current intensity of 2 mA. It combined simultaneous anodal stimulation over the left STG and stimulation cathodal over the right STG. The sham stimulation was delivered for 30 seconds over the same regions. The study was performed in a double-blind randomised controlled design.

To measure the outcome, a Korean version of Western Aphasia Battery was used: spontaneous speech, auditory verbal comprehension, repetition, naming and a common score, aphasia quotient (AQ), were assessed.

ANOVA showed an extremely reliable effect ($p<0.001$) for changes in auditory verbal comprehension before and after therapy. The interaction between the time and the stimulation condition was statistically significant, although in the absence of a significant main effect of the stimulation factor. For AQ, ANOVA also showed significant changes in this measure following therapy, although, again, without significant differences between the stimulation conditions. The absence of the stimulation effect per se, while puzzling, might possibly imply that all the improvements were induced only by the behavioural training, but not by the stimulation.

From the perspective of the functional language recovery model, it is important to focus on two things. First, all the patients in this study were sub-acute. According to the recovery model, the right-hemispheric shift of the language-related activation observed at this stage has a compensatory role. Second, most of the patients were global aphasics, moderately or severely impaired. As discussed above, these patients typically have severe lesions in the left hemisphere likely making right-hemispheric recruitment the only possible way for functional recovery. Hence, the application of cathodal (i.e. inhibitory) tDCS in this particular group of patients seems neither beneficial nor even reasonable.

A similar problem appears in Kang et al., 2011, where a cathodal tDCS was applied to the right homologue of Broca's area. The researchers suggested that this stimulation would potentially improve picture naming in patients with aphasia. The sample included 10 chronic patients with different types of aphasia, all after a single left hemispheric stroke. They underwent a double-blinded randomised sham-controlled study combining tDCS with speech training. For the real stimulation condition, 5 sessions of cathodal 2-mA tDCS, applied for 20 minutes over the right Broca's area homologue, were performed. For the sham condition, the same design was used but the current was delivered for 1 minute only.

The therapy design was rather complex. In the real condition, the patients received cathodal tDCS *after 20 minutes* of comprehensive word-retrieval training, whilst in the sham condition they received placebo tDCS *before 10 minutes* of the same training. Hence, the order of therapy and stimulation in the experimental and control groups is not matched. The authors did not explain why they chose such a design.

The Korean version of the Boston Naming Test was used as an outcome measure. Naming accuracy and response times were assessed. Statistical analysis using ANOVA showed a significant main effect for changes in accuracy ($F(1, 9) = 6.02$; $P < 0.05$), but no significant effects related to the stimulation conditions. No statistically significant changes in reaction times were found. In line with the analysis of the previous study, this might be explained by the predominant effect of training rather than stimulation on the language recovery. Hence, this study also does not provide any evidence regarding the putative efficiency of the right-hemispheric cathodal tDCS for language improvements in aphasics.

In Floel et al., 2011, the sample consisted of 12 chronic anomic aphasia patients with different lesion sites. The authors' hypothesis was that anodal tDCS could provide better improvements than cathodal or sham conditions. To test it, both anodal and cathodal stimulation conditions were used. A

1-mA stimulation was applied for 20 minutes over the right temporo-parietal cortex. The treatment consisted of 3 consecutive picture naming training phases, each combined with a different stimulation condition: anodal, cathodal or sham. The order of conditions was randomized across patients. Each condition was applied over 3 consecutive days, with a 2-hour naming session each day. As an outcome measure, the naming ability for trained objects immediately after training and 2 weeks later was used.

The results showed improvements in naming after the training from 0% correct responses at the baseline to a mean of 83% correct responses. Authors also reported paired t-tests showing better improvements in naming after the anodal condition rather than after the cathodal or the sham stimulation. However, the outcome measure scheme (result was measured on the treatment items) does not allow a conclusion about the tDCS-intervention efficiency to be made as it is hardly possible to disentangle the stimulation effect and the training effect.

Vines et al., 2011 provide somewhat more promising results of application of anodal tDCS over the anterior regions of the right hemisphere. This study involved six patients with moderate-to-severe chronic non-fluent aphasia, all after a single left-hemispheric stroke. The sample, whilst small, was very heterogeneous with respect to the age and lesion volume; furthermore, one of the patients was ambidextrous, another one was bilingual. These patients underwent a double-blind randomized controlled study. They took part in short sessions of melodic intonation therapy combined with anodal tDCS. tDCS was applied to the right posterior IFG for 20 minutes with the current intensity of 1.2 mA. Each condition was applied in three consecutive sessions for each participant. The order of sessions was counterbalanced. The stimulation started five minutes after the beginning of the session and lasted five minutes after its end. The authors hypothesized that this treatment protocol could provide improvements in speech production and fluency. As an outcome measure, the patients performed verbal fluency tasks during the last 5 minutes of the stimulation. The authors used a special measure to calculate the rate of speech in a verbal fluency task (the production of verbal sequences). A statistical analysis of the results showed better improvements in speech rate for the anodal condition rather than for the sham one, which is remarkable considering the small sample size ($t(5)=3.22$, $p=0.02$). This result is in line with our previous discussion of the impact of tDCS over the right hemisphere on the language recovery. As mentioned, in moderate-to severe aphasics - exactly the kind of patients investigated in this study - the right hemisphere probably becomes more functional. This particularly implies that excitatory stimulation of the right hemisphere, for example,

using anodal tDCS, might cause improvements in language functions. This is what was demonstrated in this study, the last one in the body of experiments we review here.

The results of studies using right-hemispheric tDCS are even less consistent than those focused on the left hemisphere and do not provide a cohesive pattern. There is also a dearth of such studies in general. Particularly the role of cathodal and anodal stimulation modes seems to be controversial. We may conclude that the anodal, excitatory stimulation of the anterior right-hemispheric language areas, particularly the IFG, might provide improvements in expressive language in some patients, namely moderate-to-severe. This is in line with one suggestion discussed above that right-hemispheric activity has a higher functional significance in more severe aphasia cases (Anglade et al., 2014). Future investigations are therefore needed to verify any effects of right hemispheric stimulation, particularly with respect to the efficacy of cathodal and anodal stimulation modes and the role of the right hemisphere in post-stroke language recovery at different stages.

General Discussion

Below, we highlight some general ideas and observations based on the review of the studies above. Most of these studies do not demonstrate significant group effects of tDCS application in aphasia patients, or these effects are weak. This can be partially explained by the heterogeneity of the samples with respect to many characteristics: aphasia type severity, term post-stroke, age of participants, lesion site and size, sometimes handedness and language background. This makes individual variability a crucial factor that may impact the efficacy of tDCS application. Most of the studies do not take into account such factors as the compatibility of tDCS protocols or outcome measures with the patients' individual characteristics. Because of these multiple methodological confounds and of the shortage of available data in general, a reliable overarching conclusion about tDCS efficacy in aphasia treatment is difficult, if not impossible, to be drawn at this time.

One way to address this issue is to take into account the ideas provided by the model of bilateral neuroplastic reorganization (Saur et al., 2006; Anglade et al., 2014). This model postulates that the role of the left and the right hemisphere in language recovery is different and depends on the recovery stage, lesion site, severity and type of impairment. These factors do not seem to have been taken into account in most of the studies we reviewed. We made a precise investigation of the data presented in these articles based on the functional reorganization model. The results of this investigation suggest that, at least in some studies, the observed low effects of tDCS might be explained by inconsistency between tDCS protocols used and certain lesion locations, aphasia types

and the severity of language impairments in different patients within one study sample. This causes a stratification of samples due to the patients' various outcomes. Different subgroups appear within samples, including subgroups of best-responders, who are the most interesting both from theoretical and practical points of view. But any effect of language improvements observed in them might become statistically insignificant against the background of the whole sample. The other possible reason why positive outcomes are not observed consistently could be the use of outcome measures which are not relevant for patients' language impairments. Namely, most of the studies we reviewed used variations of a picture naming test, regardless of aphasia type and lesion location. Some notable exceptions, for example, a study by Marangolo, 2013, with a relatively homogenous sample of mild-to-moderate aphasic patients, with stimulation targeted to the area associated with their main deficit and with outcome measures relevant to this main deficit, only support this idea: the effect of tDCS depends on the specificity of the functional organization of the language networks in the brain in particular groups of patients. Hence, well-designed studies, which take into account the functional heterogeneity of tDCS-target areas and the type and severity of language impairments, are required to find any reliable evidence of efficiency of tDCS for patients with aphasia. That said, some general remarks can be made on the basis of the studies reviewed above. Our analysis has provided arguments for the hypothesis that the most beneficial role in post-stroke language recovery belongs to perisional left-hemispheric tDCS in mild-to-moderate cases. The role of the right hemisphere seems to be rather contradictory. One could hypothesize that in severe cases of global aphasia, an excitatory stimulation could be beneficial. This is also in line with the discussed model of plastic neural reorganization, according to which the right hemisphere plays a beneficial compensatory role in the most severe cases of aphasia. The model of post-stroke language recovery we used seems to be efficient for the analysis of outcomes of these studies. Still, the influence of various individual and neural factors, including general, language-unspecific ones, needs to be investigated in more detail in future studies. More studies are required, which could focus on a range of physiological and neuroanatomic factors influencing post-stroke recovery. For example, in Campana et al., 2015, a voxel-based lesion-symptom mapping analysis was performed on a sample of twenty chronic non-fluent aphasic patients after a left-hemispheric stroke. They underwent a speech-language therapy combined with anodal tDCS over the left frontal areas. One of the goals of this study was to find predictors of better response to tDCS. The authors reported that anatomical integrity of such subcortical structures as superior and inferior longitudinal fasciculi, the insula and the basal ganglia were crucial predictors of better outcomes.

Equally importantly, further studies need to be carried out on larger samples of subjects. Such studies could be improved by using samples that are more homogeneous with respect to aphasia type, severity, term post-stroke, lesion location and size etc. As already emphasised, a precise analysis of individual differences and their possible impacts on tDCS effects must always be done. Finally, for making reliable conclusions about the neurophysiological effects of tDCS during post-stroke recovery, future studies would benefit from using precise functional neuroimaging data, which could characterise spatio-temporal patterns of language-related brain activity and correlated neurophysiological indices of recovery with behavioural and clinical outcome measures.

Conclusions

Although some studies of tDCS in patients with post-stroke aphasia provide results suggesting the potential efficacy of this procedure, various confounds and limitations of many studies in this field do not allow a reliable conclusion regarding the therapeutic potential of this technique to be made. The model of bilateral reorganization of language neural networks provides some valuable ideas about the roles of the left and the right hemispheres, and the anterior or posterior language areas within each hemisphere, in language recovery. These roles might be different depending on the lesion site, the severity of aphasia and the stage post-stroke. From this perspective, it is crucial to stratify patients with aphasia into different groups according to these parameters. Such a stratification could be helpful for the precise evaluation the of therapeutic effects putatively induced by tDCS. For this purpose, an accurate investigation of individual patient data is paramount. Further studies will require neuroimaging data on the recovery process in post-stroke aphasia, allowing a more direct assessment of the neural dynamics underpinning language function during the recovery process in order to understand the mechanisms driving language recovery at different stages. This knowledge is of a crucial importance for understanding the mechanisms which impact tDCS on language functioning in the brain and for constructing efficient stimulation protocols for clinical applications.

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References

Anglade, C., Thiel, A., & Ansaldo, A. I. (2014). The complementary role of the cerebral hemispheres in recovery from aphasia after stroke: a critical review of literature. *Brain Injury*, *28*(2), 138-145.

Ardila, A. (2014). Aphasia handbook. *Miami, FL: Florida International University*.

Baker, J. M., Rorden, C., & Fridriksson, J. (2010). Using transcranial direct-current stimulation to treat stroke patients with aphasia. *Stroke*, *41*(6), 1229-1236.

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Partially non‐linear stimulation intensity‐dependent effects of direct current stimulation on motor cortex excitability in humans. *The Journal of physiology*, *591*(7), 1987-2000.

Bindman, L. J., Lippold, O. C. J., & Redfearn, J. W. T. (1964). The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long‐lasting after‐effects. *The Journal of physiology*, *172*(3), 369-382.

Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., & Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *International Journal of Neuropsychopharmacology*, *14*(8), 1133-1145.

Campana, S., Caltagirone, C., & Marangolo, P. (2015). Combining voxel-based lesion-symptom mapping (VLSM) with A-tDCS language treatment: predicting outcome of recovery in nonfluent chronic aphasia. *Brain stimulation*, *8*(4), 769-776.

Elsner, B., Kugler, J., Pohl, M., & Mehrholz, J. (2013). Transcranial direct current stimulation (tDCS) for improving aphasia in patients after stroke. *The Cochrane database of systematic reviews*, *6*.

Flöel, A., Meinzer, M., Kirstein, R., Nijhof, S., Deppe, M., Knecht, S., & Breitenstein, C. (2011). Short-term anomia training and electrical brain stimulation. *Stroke*, STROKEAHA-110.

Fridriksson, J., Richardson, J. D., Baker, J. M., & Rorden, C. (2011). Transcranial direct current stimulation improves naming reaction time in fluent aphasia. *Stroke*, *42*(3), 819-821

Grefkes, C., & Ward, N. S. (2014). Cortical reorganization after stroke: how much and how functional?. *The Neuroscientist*, *20*(1), 56-70.

Hamilton, R. H., Chrysikou, E. G., & Coslett, B. (2011). Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. *Brain and language*, *118*(1), 40-50.

Hunter, M. A., Coffman, B. A., Trumbo, M. C., & Clark, V. P. (2013). Tracking the neuroplastic changes associated with transcranial direct current stimulation: a push for multimodal imaging. *Frontiers in human neuroscience*, *7*.

Johansen-Berg, H., & Duzel, E. (2016). Neuroplasticity: Effects of Physical and Cognitive activity on brain structure and function. *NeuroImage*, *131*, 1.

Kang, E. K., Kim, Y. K., Sohn, H. M., Cohen, L. G., & Paik, N. J. (2011). Improved picture naming in aphasia patients treated with cathodal tDCS to inhibit the right Broca's homologue area. *Restorative neurology and neuroscience*, *29*(3), 141-152.

Lee, S. Y., Cheon, H. J., Yoon, K. J., Chang, W. H., & Kim, Y. H. (2013). Effects of dual transcranial direct current stimulation for aphasia in chronic stroke patients. *Annals of rehabilitation medicine*, *37*(5), 603-610.

Lefaucheur, J. P., Antal, A., Ayache, S. S., Benninger, D. H., Brunelin, J., Cogiamanian, F., ... & Marangolo, P. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology*, *128*(1), 56-92.

Liebetanz, D., Nitsche, M. A., Tergau, F., & Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC- stimulation- induced after- effects of human motor cortex excitability. *Brain*, *125*(10), 2238-2247.

Marangolo, P., Fiori, V., Calpagnano, M. A., Campana, S., Razzano, C., Caltagirone, C., & Marini, A. (2013). tDCS over the left inferior frontal cortex improves speech production in aphasia. *Frontiers in Human Neuroscience*, *7*.

Monte-Silva, K., Kuo, M. F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain stimulation*, *6*(3), 424-432.

Monti, A., Cogiamanian, F., Marceglia, S., Ferrucci, R., Mameli, F., Mrakic-Sposta, S, Vergari, M., Zago, S., Priori, A. (2008). Improved naming after transcranial direct current stimulation in aphasia. J. *Neurol.Neurosurg.Psychiatry 79*, 451–453.

Monti, A., Ferrucci, R., Fumagalli, M., Mameli, F., Cogiamanian, F., Ardolino, G., & Priori, A. (2013). Transcranial direct current stimulation (tDCS) and language. *J Neurol Neurosurg Psychiatry*, *84*(8), 832-842.

Nias, D. K. (1976). Therapeutic effects of low-level direct electrical currents. *Psychological bulletin*, *83*(5), 766.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of physiology*, *527*(3), 633-639.

Nitsche, M.A., Paulus, W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 2001; 57:1899-901.

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*, *57*(10), 1899-1901.

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., ... & Pascual-Leone, A. (2008). Transcranial direct current stimulation: state of the art 2008. *Brain stimulation*, *1*(3), 206-223.

Polanowska, K. E., Leśniak, M. M., Seniów, J. B., Czepiel, W., & Członkowska, A. (2013). Anodal transcranial direct current stimulation in early rehabilitation of patients with post-stroke non-fluent aphasia: a randomized, double-blind, sham-controlled pilot study. *Restorative neurology and neuroscience*, *31*(6), 761-771.

Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain research bulletin*, *72*(4), 208-214.

Priori, A. (2003). Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. *Clinical Neurophysiology*, *114*(4), 589-595.

Rush, S., & Driscoll, D. A. (1968). Current distribution in the brain from surface electrodes. *Anesthesia & Analgesia*, *47*(6), 717-723.

Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., & Weiller, C. (2006). Dynamics of language reorganization after stroke. *Brain*, *129*(6), 1371-1384.

Shah, P. P., Szaflarski, J. P., Allendorfer, J., & Hamilton, R. H. (2013). Induction of neuroplasticity and recovery in post-stroke aphasia by non-invasive brain stimulation. *Frontiers in human neuroscience*, *7*.

Venkatakrishnan, A., & Sandrini, M. (2012). Combining transcranial direct current stimulation and neuroimaging: novel insights in understanding neuroplasticity. *Journal of neurophysiology*, *107*(1), 1-4.

Vines, B. W., Norton, A. C., & Schlaug, G. (2011). Non-invasive brain stimulation enhances the effects of melodic intonation therapy. *Frontiers in psychology*, *2*.

Volpato, C., Cavinato, M., Piccione, F., Garzon, M., Meneghello, F., & Birbaumer, N. (2013). Transcranial direct current stimulation (tDCS) of Broca's area in chronic aphasia: a controlled outcome study. *Behavioural brain research*, *247*, 211-216.

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