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Transcranial Direct Current Stimulation as a Tool to Induce Language Recovery in Patients with Post-Stroke Aphasia

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In recent years, possible therapeutic effects of transcranial direct current stimulation (tDCS) have been widely investigated in studies dealing with different types of neural pathologies. Initially, tDCS was applied for treatment of patients with motor stroke; later on, it was introduced into studies of patients with Alzheimer's disease, multiple sclerosis, Parkinson's disease, schizophrenia, and post-stroke aphasia. Recent reviews of tDCS application in patients with post-stroke aphasia did not provide coherent evidence on the tDCS efficiency. There were no uniform protocols of stimulation used, patients' selection criteria were highly divergent, and the reports of treatment outcomes varied dramatically. In this review, we will 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 the qualitatively different patterns of brain activity to accompany post-stroke aphasia recovery, a number of physiological factors should be taken into account to choose optimal tDCS parameters. With this in mind, we assess results of ten studies applying tDCS in post-stroke aphasia treatment, and, based on this analysis, suggest directions for further research in this rapidly developing field.

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

Introduction: tDCS as a Therapeutic Method. Electrical currents were first used for treatment in clinical medicine more than two centuries ago [Aldini, 1804]. However, experimental evidence of the impact of electrical currents on the brain excitability was obtained only in the 20th century. For example, a study by Bindman [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 the rat brain lasting about 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 the 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., 2034; Elsner et al., 2016].

The tDCS procedure is carried out with a battery-driven device. A number of manufacturers produce devices with a variable degree of customization of stimulation parameters (such as current intensity, shape, duration, or even their complex patterns) that can be applied. 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

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two foci, although this procedure is going out of practice. The size of the electrodes varies, e.g., 5 × 5 cm, 5 × 7 cm, etc. 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], the tDCS does not have any severe adverse effects. Subjects mostly report such feelings as tingling, itching, sometimes headache, pain or burning sensation during the stimulation procedure. However, all of the adverse effects recorded are short-term.

The physiological effects of tDCS application are quite variable and are observed at different levels of neural functioning: from a neurochemical level to a large-scale connectivity [Hunter et al., 2013]. The exact mechanisms of tDCS effects at the neural level are still under discussion. In comparison with, for example, transcranial magnetic stimulation, TMS [Pascual-Leone et al., 1998], which is considered as a means 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, the tDCS effect is considered as neuro*modulatory*. Critically, depending on the type of the active electrode, it is believed to modulate the neural activity in two different ways. Namely, based on the available experimental evidence, anodal tDCS is considered as an intervention that increases cortical excitability, while cathodal tDCS is considered as 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 for just a few seconds, it causes only short-lived online changes of cortical excitability that become extinct as soon as the stimulator is turned off [Nitsche et al., 2000]. In this study, the authors checked how the effects and after-effects of tDCS on the motor evoked potentials (MEP) of healthy subjects depend on the current intensity and the stimulation duration. They found that tDCS effects become prolonged as soon as a current intensity reaches 0.6 mA and the stimulation duration reaches 3 min. Further increase in any of these two parameters caused greater and more sustainable after-effects. In the study by Nietsche et al. [2001], the authors demonstrated that the after-effects might last up to one hour or even more. In this study, healthy subjects underwent a series of anodal tDCS protocols varying due to the stimulation duration. They found that 5 to 7 minutes of anodal tDCS resulted in a less that 5 minutes after-effect on the MEPs, while an application of anodal tDCS from 9 to 13 minutes caused an increase in MEPs lasting form 30 to 90 minutes.

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 the tDCS procedure is intensity of stimulation sessions. There are results confirming the idea that repetition of simulation sessions enhances the effects provided by application of direct currents on the cortex [Monte-Silva et al., 2013]. However, according to the results of recent research of Batsikadze and colleagues [Batsikadze et al., 2013], the cumulative effect of repetitive tDCS stimulation is not universal: not in every subject does an increase in intensity of stimulation cause an increase in its efficiency. The authors of this paper suggest that 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. Neuoplasticity is an "umbrella" term covering a variety of sustainable changes occurring in the brain at different functional levels that are caused by various internal and external factors such as salient environmental events, behavioral experience, brain injury, diseases, etc [Johansen-Berg, 2016]. Neuroplasticity is the crucial ability of the brain to change its structural and functional properties throughout time adjusting itself to either normal or pathological conditions. The tDCS is believed to be capable of inducing synaptic plasticity through long-term potentiation and long-term depression mechanisms [Liebetanz et al., 2002]. Hence, tDCS may have a therapeutic potential for treating brain dysfunctions by facilitating recovery-related plastic changes.

Neural diseases lead to specific and long-lasting changes in brain function. For example, in schizophrenia both positive (such as hallucinations and delirium) and negative (reduction of affect or abulia) symptoms are suggested to be

associated with a disturbed balance of activation between the prefrontal and temporal-parietal cortical regions [Ford et al., 2002]. That is why some studies [Brunelin et al., 2012; Mondino et al., 2015] have attempted to use the tDCS technique either to activate the left dorsolateral prefrontal cortex by using anodal stimulation or to inhibit temporo-parietal regions using cathodal one. During the stimulation procedure patients could either be at a resting state [Brunelin et al., 2012] or perform a task requiring discrimination between overt and covert self-produced speech ("source-monitoring task" [Mondino et al., 2015]). The first study showed a significant reduction in the level of auditory-verbal hallucinations in a real stimulation group compared to the sham one after tDCS procedures. The same effect was found in the second study, and this reduction was correlated with source-monitoring improvements.

Another example is the treatment of depressive disorders. In this case, the goal of tDCS application is to restore the activation balance between the left and the right dorsolateral prefrontal cortex. To that end, anodal stimulation of the left dorsolateral prefrontal cortex is combined with cathodal stimulation of the right dorsolateral prefrontal cortex (for a review, see [Brunoni et al., 2012]). Although the review reports the "antidepressant effect" of stimulation compared to sham, the effect size is moderate: 0.74.

Among the most obvious tDCS targets for neuroplasticity-related application might be the case of post-stroke patients with upper-limb impairments. Functional MRI studies (for a review, see [Grefkes et al., 2014]) provided convincing evidence demonstrating that the interhemispheric patterns of brain activation during movements of affected and nonaffected hands underwent dramatic changes throughout consecutive stages of post-stroke recovery. Initially, within a few days following stroke, movements of the affected hand produced a general reduction of motor-related BOLD-signal in the motor networks of both the ipsilesional and contralesional hemisphere. Within the next 10 days, motor-related activation gradually increased in both hemispheres over and above the levels observed in healthy controls and thus was associated with a stronger bilateralization of fMRI-BOLD activation. After 4 months, this "overactivation pattern" returned to a normal one concurrently with improvements in the hand motor functions. However, in case of unsuccessful recovery, there was no normalization of pathologically enhanced brain activation over time. Importantly, increases in neural activity in the first weeks after stroke significantly correlated with better motor recovery during that period. To the contrary, at the chronic phase, a decrease of "overactivation" correlated with better outcome.

A valuable insight comes from studies where repetitive transcranial magnetic stimulation (TMS) was used to suppress activity in the contralesional hemisphere. In these studies such a suppression is expected to influence, via interhemispheric interaction, the ipsilesional primary motor area and to provide enhancement in upper limb training [Avenanti et al., 2012; Seniow et al., 2012; Stagg et al., 2012]. However, there is also an increasing number of studies reporting absent repetitive TMS (rTMS) effects in stroke patients (for a review, see [Rehme et al., 2012]). These inconsistent results suggest that the contribution of contralesional cortical motor areas to motor recovery varies and might be even absent in some patients. Interestingly, some other TMS studies suggest a functional role for the contralesional hemisphere in the control of the affected hand, but only in patients showing poor recovery processes [Johansen-Berg et al., 2002; Fridman et al., 2004].

Ignoring this evidence, tDCS application in motor stroke patients at the chronic phase follows the goal either to increase ipsilesional activity of the motor cortex or to decrease contralesional activity in homologous motor areas, or both [Rossi et al., 2013; Allman et al., 2016; Khedr et al., 2013]. Still, most of these studies demonstrate a lack of evidence for any recovery effects provided either by anodal or cathodal tDCS [Lefaucheur et al., 2017].

This model of post-stroke functional changes of bilateral activity is obviously also applicable to tDCS investigations of language recovery in aphasia. Aphasia is among the most important and debilitating stroke consequences. The basic model used in aphasia studies is that of interhemispheric competition between the residual language areas in the damaged left hemisphere and the intact right hemisphere [Hamilton et al., 2011]. The goal of tDCS application in this case is to change the activation pattern of the language networks to make it more functional. In this paper, we aim at focussing on the efficiency of tDCS application in post-stroke aphasia rehabilitation. Before doing this, let us first briefly consider aphasia and its recovery more generally.

Brain Plasticity in Post-Stroke Aphasia. Aphasia is a disorder common for patients with a left-hemispheric stroke [Ardila, 2014]. Depending on lesion location, aphasic patients can have difficulties in language production, language comprehension or in both of them. The severity of these dysfunctions can also be different. Typical production or/and comprehension dysfunctions in aphasic patients usually demonstrate dynamics across three stages following stroke: acute, subacute, and chronic. The definition of terms of these stages varies across studies and is usually given approximately. The acute stage begins just after the stroke and lasts for about 2 weeks. The subacute stage follows the acute stage and lasts up to 4 months after the stroke. The chronic stage begins after the subacute stage if complete recovery is not reached by that time [Anglade et al., 2014].

An fMRI study by Saur and colleagues [Saur et al., 2006] attempted to discover the relation between functional changes occurring in the post-stroke brain across these stages and language improvements in aphasic patients. The authors found significant clinical improvements in the language function between all three stages of the recovery: acute, subacute and chronic. Functional MRI investigation showed changes in language-related activity (BOLD-

signal) in an auditory comprehension task across the recovery stages and in comparison with the norm. Namely, the results demonstrated that bilateral language-related activity in aphasic subjects decreased in the acute stage and increased in the subacute stage compared to healthy controls. The highest increase at the subacute stage was observed in the left and right inferior frontal gyri as well as in the dorsal frontal regions (probably the supplementary motor area, SMA). As for the chronic stage, no differences in language-related brain activation patterns between aphasia and the norm were found. The authors also investigated the dynamics of language-related brain activity across stages. They found increases in brain activity between the acute stage and both subacute and chronic stages, while between the latter two phases the brain activity decreased. Finally, analysis of correlations between clinical tests and fMRI data found only one significant correlation: this was a correlation of relative improvement between the acute and subacute stages and neural activation in the SMA and the right inferior frontal gyrus (IFG), including the right insular cortex. To sum up the results obtained in the study [Saur et al., 2006], we highlight that the pattern of brain language-related activity in post-stroke aphasics has its own dynamics across recovery stages. Brain activity decreases bilaterally in the acute stage; later, in the subacute stage, it increases bilaterally, especially in the left and right IFG and SMA. This change correlates significantly with clinical language improvements. In the chronic stage, the language activation peak shifted back to the left hemisphere. The authors report that this change was also related to language improvements, although these results were less significant. In brief, this study showed that bilateral brain language network reorganizes after stroke and this reorganization is connected with improvements in the language function.

There are several hypotheses explaining these processes of the post-stroke interhemispheric reorganization, or "re-mapping," and the relation of these changes to the behavioral language improvement. A review by Hamilton and colleagues [Hamilton et al., 2011] summarized the findings of many studies in *three basic hypotheses*: (1) the perilesional hypothesis language recovery is the result of the reactivation in spare language areas adjacent to the lesion [Meinzer et al., 2008; Szaflarski et al., 2013]. (2) The laterality-shift hypothesis proposes that the main recovery mechanism is a shift of language functions to the homotopic areas in the right hemisphere [Winhuisen et al., 2005; Turkeltaub et al., 2012]. On the contrary, (3) the disinhibition hypothesis postulates that post-stroke activity in the right hemisphere is caused by the loss of transcallosal inhibition and might be even deleterious for language recovery [Blank et al., 2003; Thiel et al., 2006].

This list of diverse hypotheses shows that the exact roles of the left and the right hemispheres in the aphasia recovery remain unclear. To understand their roles correctly, one should probably look for some additional variables influencing the recovery process. anglade and colleagues [anglade et al., 2014] attempted to identify the relationships between changes in the activation patterns and clinical dynamics, considering additional factors. in their review, these authors suggest that the right-hemispheric recruitment is effective only in a critical time window during the recovery after the left-hemispheric stroke. its efficiency varies depending on the lesion extent. namely, the shift of the activation balance towards the right hemisphere may be beneficial in the more severe cases with extended left-hemispheric damages, while in mild to moderate cases the main role in the recovery belongs to the left hemisphere.

Application of tDCS in Post-Stroke Aphasia. 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]. The authors of these meta-analyses focus mainly on the methodological aspects of the studies such as:

– Was double-blind randomized sham-controlled design used in the study?

– Were the exclusion and inclusion criteria presented in the paper?

– What was the size of the patient sample?

– What outcome measures were used?

– What was the statistical significance of the results obtained?

– Was a follow-up assessment performed?

In brief, the results of the studies reviewed by these papers do not allow one to make a reliable conclusion about tDCS effectiveness in aphasia. There are in general rather few studies on this issue (the largest number is 21 studies in the review [Monti et al., 2013]) and evidence of the therapeutic effects of tDCS provided in them is insufficient.

Beyond such obvious limitations as the small sample sizes, the inconsistency in the results was related to heterogeneous designs (parallel or cross-over design, sham-controlled and uncontrolled, etc.), variability of tDCS protocols (anodal, cathodal, combined stimulation of different sites and hemispheres, different current strength and stimulation duration), and patients' 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 patients' characteristics. These methodological improvements might help make assessments of tDCS effects more reliable.

Still, this is not the only point to address in future studies and reviews. Shah and colleagues [Shah et al., 2013] note that the present studies do not provide evidence on the relation between behavioral improvements and functional changes in the brain putatively induced by tDCS. The ul-

timate goal of tDCS application is to change the patterns of activity of neural networks to achieve improvement in the language function at the behavioral level, i.e., in normal communication settings.

Some authors suggest that the recovery is generally driven by the re-activation of the perilesional left-hemispheric neural networks (for a 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. The stimulation is considered as 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, while not contradicting the previous one, focuses on the activity in the right-hemispheric language area homologues, which is commonly believed to be dysfunctional/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 inhabitation approaches: several studies have used anodal tDCS over the left hemisphere and cathodal tDCS over the right hemisphere together in the same aphasic patients. In the 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 applications of non-invasive brain stimulation for patients with a motor stroke. The motor stroke recovery is correlated with reorganization of bilateral cortical motor network [Grefkes et al., 2014]. This reorganization occurs during three consecutive stages, similar to those discussed above for aphasia: acute, subacute, 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 recovery cases, 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 subacute stage, with recruitment of the right hemispheric areas. The latter plays a compensatory role in the subacute phase, while in the chronic phase its role might be different. Then the right hemispheric involvement might be deleterious in mild to moderate cases, but in moderate to severe it could still remain compensatory [Anglade et al., 2014]. This similarity of reorganization patterns allows one to speculate that post-stroke aphasia recovery in each particular case depends on the functional contribution of activity within each hemisphere into language processing. The functional role of each hemisphere might be different depending on such individual parameters as lesion location and its functional severity and recovery stage. Taking these parameters into account is important for studies using any kind of brain stimulation, including tDCS.

In our review, we will 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 will pay attention to various factors, such as location and functional severity of lesion and recovery stages of patients included in this or that study sample. 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 a probable impact of these factors on the interhemispheric activation balance, which, as discussed above, could be the main recovery factor. This approach might help to explain the lack of consistent evidence of tDCS efficiency found in previous reviews. Such an analysis of patients' individual characteristics might help uncover the variability of single patient outcomes, which can impact the averaged group effect. We will 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 a study by Fridriksson and colleagues [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 application 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), the anodal electrode was placed over the left posterior perilesional areas, while 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 of the stimulation condition used. Treatment outcome was measured using the patients' performance in the 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 the 1-tailed Wilcoxon signed rank test after exclusion of outliers. The results of the analysis made by the authors do not allow one to make a reliable conclusion about the tDCS effects on the response times in the object naming task, 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 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; the time post-stroke varied from 10 to 150 months; the sample consisted mostly of quite elderly participants. This variability may be considered as a weak point of this study since aphasia is a disorder with a well-known high individual variability in language impairments and 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 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 yet heterogeneous sample is analyzed. Overall, the inconsistencies in the design of the study by Fridriksson and colleagues, 2011, do not allow one to analyze properly the functional significance of the anodal tDCS application to the left posterior brain regions in this particular sample.

In a study by Baker and colleagues [Baker et al., 2010], 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, the 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 as well as 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 picture naming task with a 1-mA anodal tDCS stimulation delivered 20 min per day during 5 consecutive days. 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 an outcome measure taken just before, just after one week after completion of the therapy. It was assessed for both trained and untrained picture items.

Analysis performed by 2 × 2 repeated-measures ANOVA for naming of 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. As 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 localized 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 causes greater language improvements than attempts to stimulate speech cortical areas located far away from the lesion.

Different problems arise while one considers the results obtained by Volpato and colleagues [Volpato et al., 2013]. The main goal of their study was actually to find whether an offline tDCS affects recovery of the language function in any way. Offline tDCS is a protocol when stimulation is not combined with any kind of behavioral 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, terms post-stroke, and types of aphasia. Still, 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 the other one with 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 the contralateral supraorbital area. The blinding was done only for the person making outcome measures.

As an outcome measure, the authors used naming task, but in contrast with the previous studies, it included both object and action naming. The task was carried out in total three times: two weeks before the tDCS course, and just before and just after it. A new list of items was used for every testing 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 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. A 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 be-

tween the pre- and post-intervention performance to show improvements. Still, the use of just a single outcome measure, a naming ability, for a sample of different aphasics does not allow performing 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 real and sham groups. As previously mentioned, tDCS-induced effect 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 reached by several patients in the sample could be simply induced by training, and the results presented in the study do not allow one to analyze 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 subacute stage and is almost over at the chronic stage. To address tne tDCS potential to assist recovery before the chronic stage sets in, a study by Polanowska and colleagues [Polanowska et al., 2013] assessed patients with acute and subacute 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, and lesion location and volume. Patients underwent tDCS over the 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 demographic 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 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.

As a result, patients in both 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. As for the response times, improvements (in terms of the effect size) were observed 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. Still, U-criteria did not show statistically significant differences between the real and the sham group either immediately after therapy or at the follow-up. The authors interpret their result as a weak evidence of efficiency of anodal left-hemispheric tDCS for facilitating behavioral improvements in aphasic patients. As the sample was very heterogeneous, the authors tried to investigate the probable impact of different demographic and clinical parameters on the recovery. They consequently limited the sample to mild to moderate subacute patients without a large lesion. It is remarkable that this analysis revealed a tendency for a correlation with better improvements in a subgroup of patients with a term post-stroke 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 subacute stage have the highest recovery potential. Still, the recovery at this stage is more correlated with the right-hemispheric overactivation [Saur et al., 2006] rather than with the left-hemispheric underactivation. This can explain the weak tDCS-induced improvements of the potential best-responders group in comparison with a sham condition: possibly, an excitatory tDCS applied to the right hemisphere could have been more beneficial in this particular subgroup.

Such an approach to an accurate investigation of more homogeneous sub-groups of aphasic patients might indeed be quite beneficial. Particularly interesting could be investigation of 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 a study by Marangolo [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 during 5 consecutive days of a 2-week therapy course. A sham condition was applied to half of 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 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 across the patients was localized in the capsula externa, the claustrum and the putamen. The speech therapy for these patients included a 2-h daily conversation with a speech therapist, during which videoclips 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

hypothesized that application of anodal tDCS to Broca's rather than to Wernicke's area would lead to greater improvements in quality and quantity of the expressive speech.

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

This study demonstrates the effectiveness of accurate sample collection and optimal stimulation site selection. This goes in line with the suggestion we made below that given the high individual variability of aphasic patients it is absolutely crucial to form homogeneous patient groups. Such an approach allows obtaining detectable and significant results, as this study shows. Otherwise, in heterogeneous samples, any improvement effects in particular subgroups may be smeared or even cancelled out after averaging of 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 and colleagues [Monti et al., 2008] collected a sample of eight 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. Computerized picture naming task was used as an outcome measure, taken before and after each session. The naming accuracy and response times were assessed. 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, while 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 be not quite homogeneous, does not allow a reliable conclusion about the nature of physiological effect obtained.

Second, the 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 the 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 conclusion of the left-hemispheric tDCS efficiency in post-stroke aphasia. Most of the effects demonstrated are weak or, in some case, do not even reach statistical significance. However, 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 goes in line with one of the hypotheses explaining bilateral language networks reorganization: re-activation of the intact perilesional areas is the main factor driving language recovery in the transition from the subacute to the chronic stage.

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

Right-Hemispheric tDCS in Aphasia. You and colleagues [You et al., 2011] applied tDCS in a group of subacute aphasia patients in two conditions: anodal tDCS to the left STG or cathodal tDCS to the contralateral (right) STG. The sample consisted of 21 subacute 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 and 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 cathodal stimulation over the right STG. The sham stimulation was delivered during 60 seconds over the same regions. The study was performed in a double-blind randomized 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 time and stimulation condition was statistically significant, although in the absence of a significant main effect of the stimulation factor. As for the aphasia quotient, ANOVA also showed significant changes in this measure following therapy, although again without sig-

nificant 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 behavioral training, but not by the electric stimulation.

From the perspective of the functional language recovery model, it is important to focus on the following. First, all the patients in this study were subacute. According to the recovery model, the right-hemispheric shift of the language-related activation observed at this stage plays a compensatory role. Second, most of the patients were global aphasics, moderately or severely impaired. As has already been discussed above, these patients typically have severe lesions in the left hemisphere likely making the 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 appeared in results of a study by Kang and colleagues [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 randomized sham-controlled study combining tDCS with speech training. For the real stimulation condition, five 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 10 minutes* of comprehensive word-retrieval training, while in the sham condition they received placebo tDCS *after 20 minutes* of the same training. Hence, the design of therapy and stimulation in the experimental and control groups did not match 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 another study by Floel and colleagues [Floel et al., 2011], the sample consisted of 12 chronic anomic aphasia patients with different sites of lesions. 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 during 20 min over the right temporo-parietal cortex. The treatment consisted of three 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 correct naming after the training from 0% responses at the baseline to a mean of 83% correct responses. The authors also reported paired t-tests showing better improvements in naming after the anodal condition rather than after the cathodal or sham stimulation. However, the outcome measure scheme (result was measured on the treatment items) does not allow one to make a conclusion about the tDCS-intervention efficiency as it is hardly possible to disentangle the stimulation effect and the training effect in this case.

A study by Vines and colleagues [Vines et al., 2011] provides 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, while small, was very heterogeneous with respect to the age and lesion volume; furthermore, one of the patients was ambidextrous, and 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. The tDCS was applied to the right posterior IFG during 20 minutes with a 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 5 minutes after the beginning of the session and lasted 5 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 the verbal fluency task (production of the verbal sequences). 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 goes 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 role of 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.

As seems obvious, 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 goes in line with one of the suggestions discussed above, namely that the right-hemispheric activity has 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, and sometimes handedness and language background. This makes individual variability a crucial factor that may impact the efficiency of tDCS application. Most of the studies do not take into account such factors as 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.

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] that we have described earlier in this review. 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 and severity, as well as on the 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 small effects of transcranial direct current stimulation might be explained by the inconsistency between the tDCS protocols used and certain lesion locations, aphasia types, and severity of language impairments in different patients within one study sample. This causes stratification of samples due to the patients' various outcomes. Different subgroups appear within samples, including subgroups of best responders, that are most interesting both from the theoretical and the 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 that are not relevant to the 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 and colleagues [Marangolo et al., 2013], with a relatively homogeneous 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 functional organization of the language networks in the brain in particular groups of patients. Hence, well-designed studies, which take into account functional heterogeneity of tDCS-target brain areas as well as the type and severity of language impairments, are required to find any reliable evidence of efficiency of the tDCS procedure for patients with aphasia. That said, some general remarks can be made even on the basis of the studies reviewed above. Our analysis has provided arguments for the hypothesis that the most beneficial role in the post-stroke language recovery belongs to perilesional 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 also goes 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 analysis of outcomes of these studies. Still, the influence of various neural factors, including general, language-nonspecific ones as well as individual ones, needs to be investigated in more detail in future studies. More studies are required, which could, among others, focus on the range of physiological as well as neuroanatomic factors influencing post-stroke recovery. For example, in one study [Campana et al., 2015], a voxel-based lesion-symptom mapping analysis was performed in a sample of 20 chronic non-fluent aphasic patients after a left-hemispheric stroke. They underwent 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 the anatomical integrity of such subcortical structures as superior and inferior longitudinal fasciculi, the insula, and the basal ganglia turned out to be crucial predictors of better outcomes.

Further studies need to be carried out in larger samples of subjects. At the same time, such studies could be improved by using samples that will be more homogeneous with respect to aphasia type and severity, term post-stroke, lesion location and size, etc. As already reiterated, 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 the post-stroke recovery, future studies will benefit from using precise functional neuroimaging data, which could characterize spatio-temporal patterns of language-related brain activity and correlated neurophysiological indices of recovery with behavioral and clinical outcome measures.

Conclusions. Although some studies of tDCS application in patients with post-stroke aphasia provide results suggesting the potential efficacy of this procedure, various confounds and limitations of most of the studies in this field do not allow making a reliable conclusion regarding the therapeutic potential of this technique. The model of bilateral reorganization of language neural networks provides some valuable ideas about the roles of the left and the right hemispheres, as well as the anterior or posterior language areas within each hemisphere, in the language recovery. These roles might be different depending on the lesion site and the severity and the stage of post-stroke. From this perspective, it becomes crucial to stratify patients with aphasia into different groups according to these parameters. Such a stratification could be helpful for precise evaluation 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 the language function during the recovery process, in order to understand the mechanisms driving language recovery at different stages. This knowledge is of crucial importance for understanding the mechanisms of tDCS impact on the language function in the brain as well as for constructing efficient stimulation protocols for clinical applications.

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