Neural mechanisms underlying improved new-word learning with high-density transcranial direct current stimulation

Camille Farcy [a], Lea A.S. Chauvigné [a], Marina Laganaro [c], Marion Corre [a], Radek Ptak [a], Adrian G. Guggisberg [a,b,*]

[a] *Division of Neurorehabilitation, Department of Clinical Neurosciences, University Hospital of Geneva, Av. de Beau-Séjour 26, Geneva 1211, Switzerland*
[b] *Universitäre Neurorehabilitation, Universitätsklinik für Neurologie, Inselspital, University Hospital of Berne, Berne 3010, Switzerland*
[c] *Neuropsycholinguistics Laboratory, University of Geneva, Geneva, Switzerland*

ABSTRACT

Neurobehavioral studies have provided evidence for the effectiveness of anodal tDCS on language production, by stimulation of the left Inferior Frontal Gyrus (IFG) or of left Temporo-Parietal Junction (TPJ). However, tDCS is currently not used in clinical practice outside of trials, because behavioral effects have been inconsistent and underlying neural effects unclear. Here, we propose to elucidate the neural correlates of verb and noun learning and to determine if they can be modulated with anodal high-definition (HD) tDCS stimulation. Thirty-six neurotypical participants were randomly allocated to anodal HD-tDCS over either the left IFG, the left TPJ, or sham stimulation. On day one, participants performed a naming task (pre-test). On day two, participants underwent a new-word learning task with rare nouns and verbs concurrently to HD-tDCS for 20 min. The third day consisted of a post-test of naming performance. EEG was recorded at rest and during naming on each day. Verb learning was significantly facilitated by left IFG stimulation. HD-tDCS over the left IFG enhanced functional connectivity between the left IFG and TPJ and this correlated with improved learning. HD-tDCS over the left TPJ enabled stronger local activation of the stimulated area (as indexed by greater alpha and beta-band power decrease) during naming, but this did not translate into better learning. Thus, tDCS can induce local activation or modulation of network interactions. Only the enhancement of network interactions, but not the increase in local activation, leads to robust improvement of word learning. This emphasizes the need to develop new neuromodulation methods influencing network interactions. Our study suggests that this may be achieved through behavioral activation of one area and concomitant activation of another area with HD-tDCS.

1. Introduction

Language learning and re-learning play a crucial role in activities of daily living and quality of life for both neurotypical individuals and patients with aphasia (Peñaloza et al., 2022). For neurotypical individuals, learning new languages stimulates cognitive functions, enhances memory retention, and promotes mental agility. In the case of patients with aphasia, language re-learning becomes a vital element of their rehabilitation process (Schevenels et al., 2022). By reacquiring language skills, these individuals regain their ability to express thoughts and emotions, engage in social interactions, and participate more actively in society (Basso et al., 2013; Bullier et al., 2020). However, about 60 % of patients with aphasia remain with communication

impairment despite rehabilitation (RELEASE Collaborators, 2021). New treatment options would thus be highly welcome, among them non-invasive brain stimulation is a promising approach (Hillis, 2023; Marangolo and Pisano, 2020)

Non-invasive brain stimulation such as transcranial direct current stimulation (tDCS) allows modulation of neural activity (Torres et al., 2013). tDCS is easy to transport and use and provides a low rate of side effects. This technique has already been used in aphasia, particularly in combination with behavioral therapies (Buchwald et al., 2020; Cotelli et al., 2020; Marangolo, 2020). Some studies have provided evidence for the effectiveness of anodal tDCS, in particular on language production, by stimulation of the left Inferior Frontal Gyrus (IFG) or of left Temporo-Parietal Junction (TPJ) regions in healthy volunteers but also

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patients suffering from aphasia after stroke (Cattaneo et al., 2011a; Elsner et al., 2019; Matar et al., 2020). Left IFG stimulation in combination with language training was found to be most effective for the facilitation of verb naming (Marangolo et al., 2013; Pisano and Marangolo, 2020) and stimulation of the left TPJ region for learning noun naming (Fiori et al., 2013; Shao et al., 2022) in aphasic patients. Furthermore, tDCS enhanced phonological processes in neurotypicals (Cattaneo et al., 2011a; Matar et al., 2020).

However, meta-analyses have reported variable and rather small effects of tDCS in aphasia (Ding et al., 2022; Elsner et al., 2019; Georgiou and Kambanaros, 2023). Current guidelines do not recommend tDCS for treating aphasia outside of studies (Lefaucheur et al., 2018). One of the main reasons for the unsatisfactory effects is that we do not sufficiently understand the plasticity underlying language (re-)learning and the neural processes we need to target with neuromodulation. tDCS usually aims at influencing local activity levels at the stimulated brain area. Language processing depends on local neural activation in key language areas (Catani et al., 2005; Geschwind et al., 1968). Local activation is commonly expressed as a task-induced decrease in alpha and beta power (often labeled as event-related desynchronization) (Pfurtscheller, G., Lopes da Silva, 1999). However, there is increasing evidence that the interaction within neural networks rather than local activity levels of single brain regions is key for optimal performance (Allaman et al., 2020; Guggisberg et al., 2015; Hula et al., 2020; Sadaghiani et al., 2015). This probably also applies to patients with aphasia, as patients with different lesions can exhibit similar language disorders (Fridriksson et al., 2018). This is because an extensive cortical network is involved in language processes and, therefore, the same language disorder can result from damage to different areas of this network. Furthermore, subcortical regions seem to be strongly involved in language processes such as, among others, the left putamen and the globus pallidus (Tomasi and Volkow, 2012). Indeed, greater activation of the left putamen correlates with faster phonological processing (Tettamanti et al., 2005) and appears to be one of the most affected regions in aphasic patients (Kim et al., 2021).

The brain maintains a high level of interactions among brain areas, even at rest, when it is not explicitly involved in a specific task. Resting-state interactions occurring mainly in the so-called alpha frequency band (8-13 Hz) (Guggisberg et al., 2008) are crucial for correct task performance and learning. For instance, participants with high levels of neural interactions (also called functional connectivity, FC) between the left IFG and the rest of the brain have higher performance in language production tasks (Guggisberg et al., 2015) and show greater training gains when learning new words (Nicolo et al., 2016). Moreover, patients with brain lesions due to stroke have reduced resting-state alpha-band FC, which correlates with the severity of neurological deficits (Dubovik et al., 2012; Westlake et al., 2012). In particular, a loss of FC of structurally preserved inferior frontal areas was associated with more severe aphasia. Recovery from aphasia is associated with an enhancement of FC between inferior frontal brain areas and the rest of the brain, probably reflecting a reorganization of neural connections as a neural mechanism involved in plasticity (Nicolo et al., 2015). Resting state FC is therefore an interesting neural target for therapy (Guggisberg et al., 2015; Nicolo et al., 2015), which could help improve the recovery from aphasia and contribute to the understanding of neural networks involved in language processing. Thus, the effects of non-invasive brain stimulation, including tDCS, on interactions of language networks may be crucial for inducing behavioral gains, but are currently largely unknown.

Here, we propose to elucidate the neural mechanism of the previously reported behavioral effect of anodal high-definition (HD) tDCS stimulation on verb and noun naming. To this end, we studied rare-word learning in neurotypical adults as a substitute for (re-)learning in aphasia. Exploring the principles of learning is pivotal for enhancing neurorehabilitation outcomes post-stroke and bolstering its efficacy (Kitago and Krakauer, 2013; Maier et al., 2019). Furthermore, remarkably similar principles have been uncovered governing re-learning and

retention in the lesioned brain as those observed in neurologically healthy individuals (Rapp and Wiley, 2019). Based on previous studies, we evaluated the effect of stimulation of two key nodes of the language network, the left inferior frontal gyrus (IFG) and the temporo-parietal junction (TPJ). Thereby, we investigated the effects of tDCS on two different types of neural processing: classical local activation as indexed by naming-induced alpha- and beta-power decrease in the target regions and network changes as indexed by FC. We hypothesized that anodal HD-tDCS improves rare-word learning by enhancing FC of the stimulated area in addition to inducing changes in local activation.

2. Materials and methods

2.1. Participants

A total of 36 healthy young participants, 18 males and 18 females (mean age 25 years, range 18-43) without neurological or psychiatric disease were recruited after writing informed consent. A power analysis based on the effect size of previous studies with new word learning after tDCS in healthy subjects (Cattaneo et al., 2011b) and patients (Marangolo et al., 2013) suggests that a sample size of 12 per group gives 80 % power to detect similar differences between active and sham stimulation conditions at $p<0.05$. A total sample size of 36 gives >80 % power to detect correlations of $r=0.5$ between neural and behavioral effects. All were right-handed as determined by self-report. Procedures were approved by the ethics committee of Geneva, Switzerland (project number: 2020-01624). All procedures were in accordance with international ethical standards on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. The participants were paid for their participation.

2.2. Experimental design

Participants were randomly assigned to one of the three parallel arms in equal proportion (12 participants per arm):

- HD-tDCS on the left IFG;
- HD-tDCS on the left TPJ;
- sham HD-tDCS.

The three groups were matched in terms of age (p=0.26, Kruskal-Wallis test) and sex (p=0.32, Fisher-Freeman-Halton test).

All participants underwent three sessions on three separate and consecutive days (see Fig. 1A).

The first and third sessions consisted of pre- and post-tests, respectively. During those sessions, participants performed a naming test of very low-frequency verbs and nouns (see section "Rare-word learning paradigm"), while EEG was recorded. EEG was additionally obtained during a no-task resting-state before and after the tasks on each of the three days. During resting-state recordings, participants are required to close their eyes and relax for 5 min without sleeping.

In the first session only, before the naming test, participants were familiarized with all the pictures used for the naming task. Pictures were presented one by one on a screen along with their corresponding names. Each item was presented for 3000 ms.

On the second day, participants underwent brain stimulation while performing a learning task during which they learned to name half of the nouns and verbs, counterbalanced across participants. Resting state EEG of 5 min was recorded before and after the stimulation.

2.3. Rare-word learning paradigm

We evaluated verbal learning using a rare-word learning paradigm, designed to induce learning of real but mostly unknown nouns and verbs (Fargier and Laganaro, 2020; Nicolo et al., 2016). The stimuli consisted of 100 black and white line drawings depicting object and action words.
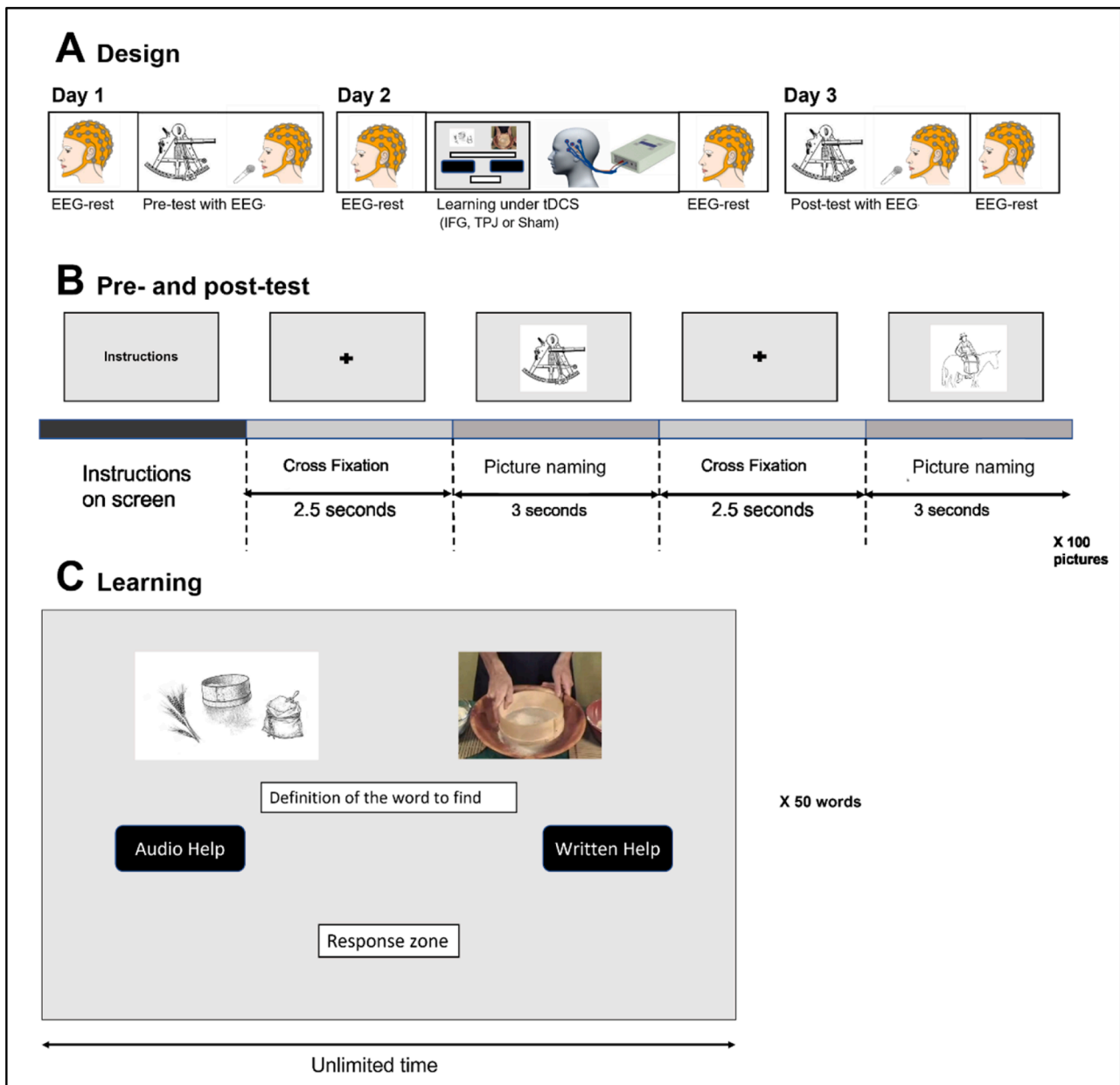
Fig. 1. Experimental design and rare-word learning paradigm. (A) Experimental design. (B) Naming task at pre and post-test. (C) Learning task at day 2 with HD-tDCS.

Words with very low lexical frequency (mean±standard devation, overall 0.22±0.86; nouns 0.43±1.18; verbs 0.02±0.04) were selected from the French database Lexique (New et al., 2004) and consisted of 50 nouns (ancient or rare objects, tools, or musical instruments) and 50 verbs (ancient actions or specialized vocabulary from sailing, agriculture, zoology, and others). Words were largely unknown at baseline (pre-test naming 14.8±9.2 out of 100),

In order to have a trained list and a control list, two lists of 50 items containing 25 nouns and 25 verbs each (lists A and B) were constituted and matched for lexical frequency (p=0.86), length in syllables (p=0.84), and phonemes (p=0.97). The control list was used at pre-test and post-test but was not learned in order to control for test-retest effects.

The pre- and post-test of day 1 and 3, respectively, consisted of a *naming task*, which allowed us to assess naming performance before and after learning (Fig. 1B). Pictures were presented on a computer screen in random order and in two separate blocks with mixed nouns and verbs.

Participants were requested to produce overtly the word corresponding to the picture as fast as possible or to overtly say "no" if they didn't know the answer. Each list of 50 words was presented twice, each time in a different order. Each item was presented for 3000 ms. Oral productions were recorded with a microphone synchronized with the presentation software (E-prime, Psychology Software Tools, Pittsburgh, USA) (Schneider et al., 2012).

On day 2, subjects performed a *learning task*, combined with tDCS in one of the 3 stimulation conditions. To facilitate learning, pictures corresponding to words of the learned list were presented as photographs and black and white line drawings along with their definition on a computer screen. The black and white drawings were the same as the ones used for the naming task in the pre- and post-test, while the photographs were additionally displayed during learning to facilitate association between the images and the corresponding words. This modification aims to enable participants to establish a connection between the visual representation and the word, enhancing the learning

process and potentially improving retention for later recall (Brennen et al., 1996; Kremin, 2018). Participants were asked to write the corresponding word on a computer keyboard. They were able to hear the spoken word and to read the correct spelling of the word by clicking on the "Audio help" or "Written help" buttons, respectively, if they needed to (Fig. 1C). They proceeded to the next item when they wrote the correct word and clicked the "Validate" button. They had no time limit for this task. The learning task was implemented in Psychopy (Peirce et al., 2019) which uses Python language. Pictures of the learned list were presented three times in pseudo random order for twenty-seven participants (9 per arm). Nine participants (3 per arm) saw the pictures of the learned list only once in order to explore whether the stimulation effect would depend on training intensity.

2.4. Behavioral outcomes

At the behavioral level, the primary endpoint was the percentage of newly learned words from pre-test (day 1) to post-test (day 3). Correct answers are defined as correct oral production to the target word within 3 s. The number of correctly named words was calculated as the average of the two blocks. Learning was expressed in percent of the maximum possible behavioral gain, i.e., the change in performance from pre- to post-test divided by the difference between the total number of words and the score in pre-test. We distinguished between two types of learned words, namely, nouns and verbs. We also evaluated the performance change of the untrained control list.

2.5. Brain stimulation

tDCS was carried out with a DC-STIMULATOR PLUS (neuroConn GmbH, Ilmenau, Germany). Participants received either left IFG stimulation, left TPJ stimulation or sham stimulation depending on their group attribution. We used an anodal high-definition (HD) montage which consists of 1 active electrode (anode) and 4 reference electrodes (cathodes), placed on the participant's skull around the active electrode. HD configurations involving 4×1 electrodes allow a more focal and intense current diffusion than classical montages (DaSilva et al., 2015). The distance between the electrodes was chosen such that the target was reached selectively but with good intensity diffusion. Indeed, an increase in the diameter of the arc increases the depth and the intensity but a reduction allows a more focal stimulation (Villamar et al., 2013). For IFG stimulation, the active anode electrode was placed on FC5, the 4 reference cathodes were located on F3, F7, C3, and T7. Regarding TPJ, the active anode electrode was on CP5, the 4 cathode electrodes were on T7, C3, P3, and P7. The current was ramped up during 30 sec to 1.7 mA and was then applied for 20 min in all participants. Originally, a current intensity of 2 mA was planned, but had to be reduced because of

difficulties of obtaining the impedance in some subjects in pilot studies due to variations in skin resistance and electrode contact quality. Variability in impedance values among participants can result in unequal current flow. A current intensity of 1.7 mA ensured stable and comparable current flow in all subjects. We simulated the current distribution resulting from these settings with SimNIBS 4, a freely available and open source software package providing a means to calculate the electric field generated by transcranial electric stimulation (Thielscher et al., 2015), see Fig. 2.

For sham tDCS, the DC current is ramped up for 30 seconds and then stopped. This strategy does not induce a change in brain activity but a subjective sensation equal to the real stimulation. The electrodes were positioned over either the IFG (half of the sham participants) or the TPJ (other half).

2.6. EEG acquisition

EEG recordings were made with an ActiCHamp (BrainVision, Gilching, Germany) system using 128 electrodes placed on the surface of the scalp to digitize signals at a sampling rate of 500 Hz. The ground electrode was positioned at Fz and we used Cz as reference electrode. Visual data inspection was made offline in Cartool (Brunet et al., 2011) to exclude epochs with movement artifacts, eye blinking and other noise. Bad channels holding prolonged artifacts were ignored from further analyses.

2.7. EEG analyses

Source localization was performed in MATLAB (The MathWorks Inc.) with the toolbox NUTMEG (https://www.nitrc.org/plugins/mwiki/index.php/nutmeg:MainPage) (Dalal et al., 2011). Lead-potential with 10 mm grid spacing was obtained using the Boundary Element Method (BEM) based on the segmented gray matter of the standard Montreal Neurological Institute (MNI) brain. An adaptive spatial filter "beamformer" was used for source localization and reconstruction of neural activity (Sekihara et al., 2004). Adaptive filter weights were computed based on the sensor covariance of the bandpass filtered data from all epochs.

Power was computed as squared absolute Fourier coefficients. Event-related power change was evaluated in order to explore oscillatory modulations of sets of neurons indicating a local activation during the denomination task (Dalal et al., 2008). We used a 200 ms long sliding Hanning window with 50 ms time steps to Fourier-transform signals. Nouns and verbs were analyzed separately. We obtained, for each participant, average power across an average of 49.9 ($\pm$0.55) artifact-free epochs (p=0.07 for difference between stimulation conditions). Power was computed at each time window for alpha (8–13 Hz)
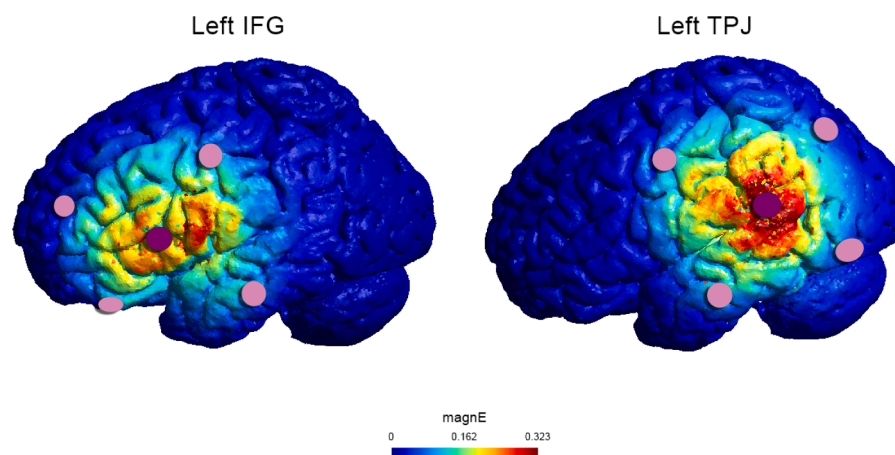

Fig. 2. Gray matter surface with the magnitude of the electric field (magnE) simulated for Left IFG and Left TPJ transcranial direct current stimulation.

and beta (13–30 Hz) frequency bands. Log transformed values were used to approximate normal distribution. A pre-stimulus baseline power from -300 to 0 ms was subtracted from all active windows.

For analysis of FC, 5 min of artifact-free resting-state EEG data were segmented into 300 epochs of 1 s duration. They were bandpass-filtered between 1 and 20 Hz using an ellipsoid infinite impulse response (IIR) forward-backward filter to obtain zero phase shift, tapered with a Hanning window and Fourier transformed. FC was quantified as the absolute imaginary component of coherence (IC) in delta (1 – 3.5 Hz), theta (3.5 – 7.5 Hz), alpha (7.5 – 13 Hz), and beta (13 – 20 Hz) frequency bands (Nolte et al., 2004). Magnitude-squared coherence is not a suitable measure for EEG FC, because it is subject to biases resulting from volume conduction of the measured potential when recording from the surface and from limitations of the spatial resolution of inverse solutions when performing source imaging (Fein et al., 1988; Guevara et al., 2005; Schiff, 2005). IC avoids overestimation biases because of sensor crosstalk, volume conduction and spatial leakage of inverse solutions (Sekihara et al., 2011) and therefore provides a more robust measure of FC. The weighted node degree (WND) was computed at each voxel as average absolute imaginary coherence with all other voxels in order to quantify global connectivity at each voxel with all other voxels (Guggisberg et al., 2015; Newman, 2004). WND can be seen as an index of the overall importance of an area in the brain network (Stam and van Straaten, 2012). Fluctuations in the signal-to-noise ratio between participants or conditions can cause variations in functional connectivity. To correct for the influence of the signal-to-noise ratio of the recordings (cleaner recordings lead to generally greater FC), we normalized the WND with z-scores: the mean WND across all voxels was subtracted from the WND at each voxel, and the result is divided by the standard deviation across all voxels.

We then computed mean power and global FC (WND) of three regions of interest (ROIs): the two main cortical nodes of the language network, left IFG and TPJ (Area 44 and Area PFm (IPL) defined with the Jülich atlas (Malikovic et al., 2019)), as well as the main subcortical node for language and learning, the lentiform nucleus (Kim et al., 2021; Tettamanti et al., 2005; Tomasi and Volkow, 2012) (left Putamen and Globus Pallidus defined with the Automated Anatomical Labelling atlas (Tzourio-Mazoyer et al., 2002)). In addition, we specifically investigated FC between the left IFG and the left TPJ and between left IFG and lentiform nucleus.

We obtained short-term training and stimulation-induced change in power and FC as the difference between before and after stimulation on day 2. Long-term change was quantified as the difference between day 1 and day 3.

2.8. Statistical analysis

Analyses were performed with the Statistics Toolbox of MATLAB (The MathWorks Inc.).

Age was compared between groups with a Kruskal-Wallis test since data were not normally distributed. Sex was compared with the Fisher-Freeman-Halton test for proportions. EEG and behavioral learning variables satisfied the assumptions of normality and parametric tests were therefore used. Behavioral data was subjected to a mixed-model-ANOVA with pre-test and post-test naming performance as dependent variable, time as within factor, and stimulation and number of training runs as between factors. In addition, learning and resting-state neural changes were compared across stimulation conditions (IFG, TPJ, sham) with ANCOVAs, which included the number of training runs (1 or 3) as a confounding covariate. For event-related power, we performed mixed-model ANCOVAs, with stimulation condition as between factor, time as within factor, and number of training runs as confounding cofactor. The mean of critical active time windows (between 300 and 500 ms after picture presentation) was used for pairwise comparisons and for correlations with learning. The Tukey-Kramer HSD was used for pairwise post-hoc comparisons in all cases. Neural changes were correlated with

learning using Pearson partial correlations, which included the number of training runs as a confounding covariate. Correlations were performed across the entire sample as whole (without distinction of the stimulation condition). They were performed separately for noun and verb learning. If correlations were present for both, a single combined learning score was used.

In our screening for neural correlates of improved learning under tDCS, we required two tests to be significant at the same time at a given ROI and frequency band: the ANCOVA indicating a difference between stimulation conditions AND the partial correlations between neural changes and learning. Usual corrections for multiple testing such as Bonferroni or false discovery rate (FDR) are not adequate in this situation, as they use separate null-hypotheses for each test and therefore neglect the required Boolean combination of two tests. To estimate the risk of finding differences between stimulation conditions and correlations with learning at the same time by pure chance, we performed a permutation test. During each of 2000 permutations, the order of the condition labels in the ANCOVA and of the learning variable in the partial correlation was scrambled and the tests repeated, using $p<0.05$ uncorrected as cutoff. We then counted the times where both tests were significant by pure chance at ANY ROI or frequency in this scrambled data. This showed that the risk of finding significant differences between stimulation conditions AND significant correlation with learning by pure chance (false positives) was low ($p = 50/2000 = 0.025$ for 2 ROIs x 4 frequency bands, $p = 84/2000 = 0.042$ for 3 ROIs x 4 frequency bands). The requirement of two different significant statistical tests at the same time at $p<0.05$, uncorrected, therefore effectively controlled for false positives due to multiple testing.

In cases where only a single statistical test was positive, a FDR of 5 % was used to correct for multiple testing.

3. Results

3.1. Behavioral effects of tDCS on word learning

Mixel-model ANOVAs on naming performance at pre- and post-tests showed a main effect of time for both verbs and nouns (Verbs: $F_{1, 30} = 76.2$, $p < 0.001$; Nouns: $F_{1, 30} = 89.2$, $p < 0.001$), but not for non-learned words ($F_{1, 30} = 2.4$, $p = 0.13$), confirming that learning took place during training. We also observed a main effect of stimulation for nouns and verbs (Nouns: $F_{2,30} = 4.8$, $p = 0.01$; Verbs: $F_{2,30} = 7.2$, $p = 0.002$), as performance was overall higher for the IFG group than for the sham group at both time points. There was a numerically small but statistically significant difference in pre-test naming performance (mean±SD for IFG 3.7±2.2, TPJ 2.4±1.8, sham 1.4±1.4, p=0.017). However, the difference became larger in the post-test (mean±SD for IFG 14.4±3.4, TPJ 10.7±5.7, sham 7.2±5.9, p=0.006). We accounted for this baseline difference with a mixed-model ANOVA demonstrating a significant interaction between time and stimulation conditions for verbs ($F_{2, 30} = 3.5$, $p = 0.044$), but not for nouns ($F_{2,30} = 1.1$, p=0.37) or unlearned words ($F_{2, 30} = 2.5$, p=0.10). Fig. 3 shows the behavioral effect of tDCS on rare word learning with the percentage of learning according to stimulation. We notice a significant difference in verb learning between the stimulation conditions (mean±SD for left IFG 50.1±15.5 %, left TPJ 37.3±23.2 %, sham 25.1±22.6 %) ($F_{2,30} = 4.59$, $p = 0.0183$). Post-hoc pairwise comparisons showed that participants receiving left IFG stimulation learned more verbs than those receiving Sham (p<0.05, Tukey-Kramer HSD), Cohen's D = 0.78. In contrast, there was no stimulation effect on noun learning (left IFG 47.5±15.7 %, left TPJ 40.1±25.4 %, sham 30.4±21.4 %) ($F_{2,30} = 2.1$, p=0.14). These results indicate an improvement of performance specifically in verb naming with stimulation of the left IFG. Performance for non-learned words did not improve and did not differ between stimulation conditions (left IFG 2.2 %, left TPJ 0.3 %, sham -1.1 %) ($F_{2,35} = 1.96$, $p = 0.16$), as expected. To explore whether the stimulation effect depended on the training dose, a subset of nine participants received low-intensity training with only a single
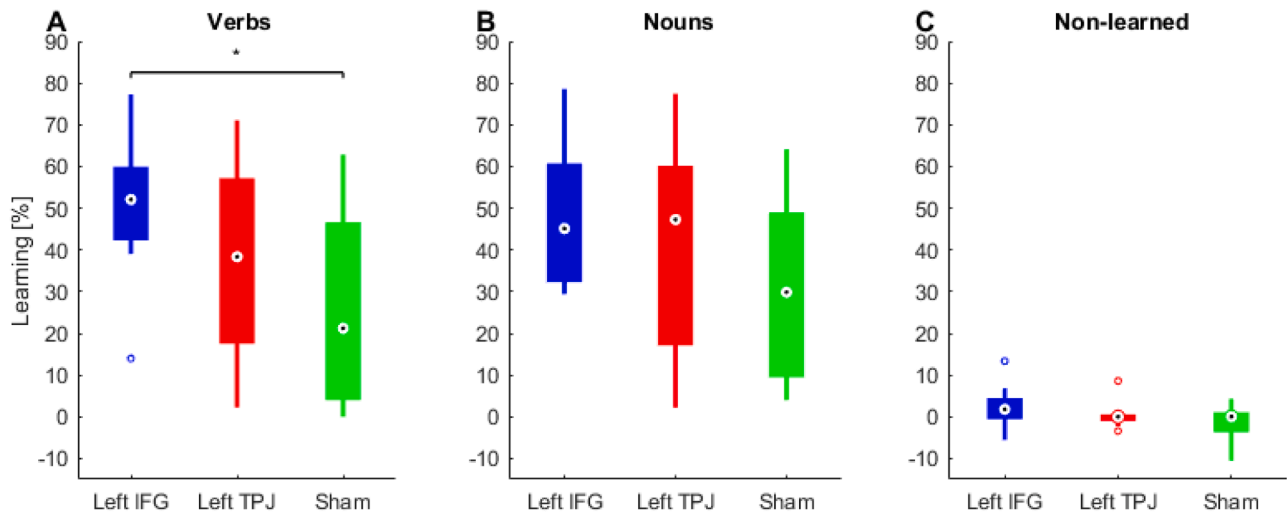
Fig. 3. Behavioral effects of tDCS on rare word learning. Learning of verbs (A), nouns (B) and non-learned control words (C) for each stimulation condition.

learning run, while the remaining twenty-seven received three runs. There was a main effect of the number of training runs on verb learning ($F_{1,30} = 13.13$, $p=0.0011$), but no interaction between the stimulation condition and the number of training runs ($F_{2,30}= 0.06$, $p=0.93$), suggesting that the stimulation effect was not dependent on the training intensity. Please note however, that this analysis of interaction was exploratory and limited by low and unbalanced sample sizes.

3.2. Local activation

The long-term influence of training under tDCS on local neural activation during naming was measured as difference in task-induced alpha and beta power from the pre-test (day 1) to post-test (day 3). First, we screened for ROIs and frequencies that showed an interaction between stimulation condition and time after presentation of either verbs or nouns. There was a trend for interaction for alpha ($F_{52,971}=1.3$, $p=0.07$) and beta ($F_{52,971}=1.3$, $p=0.056$) power change at the left TPJ
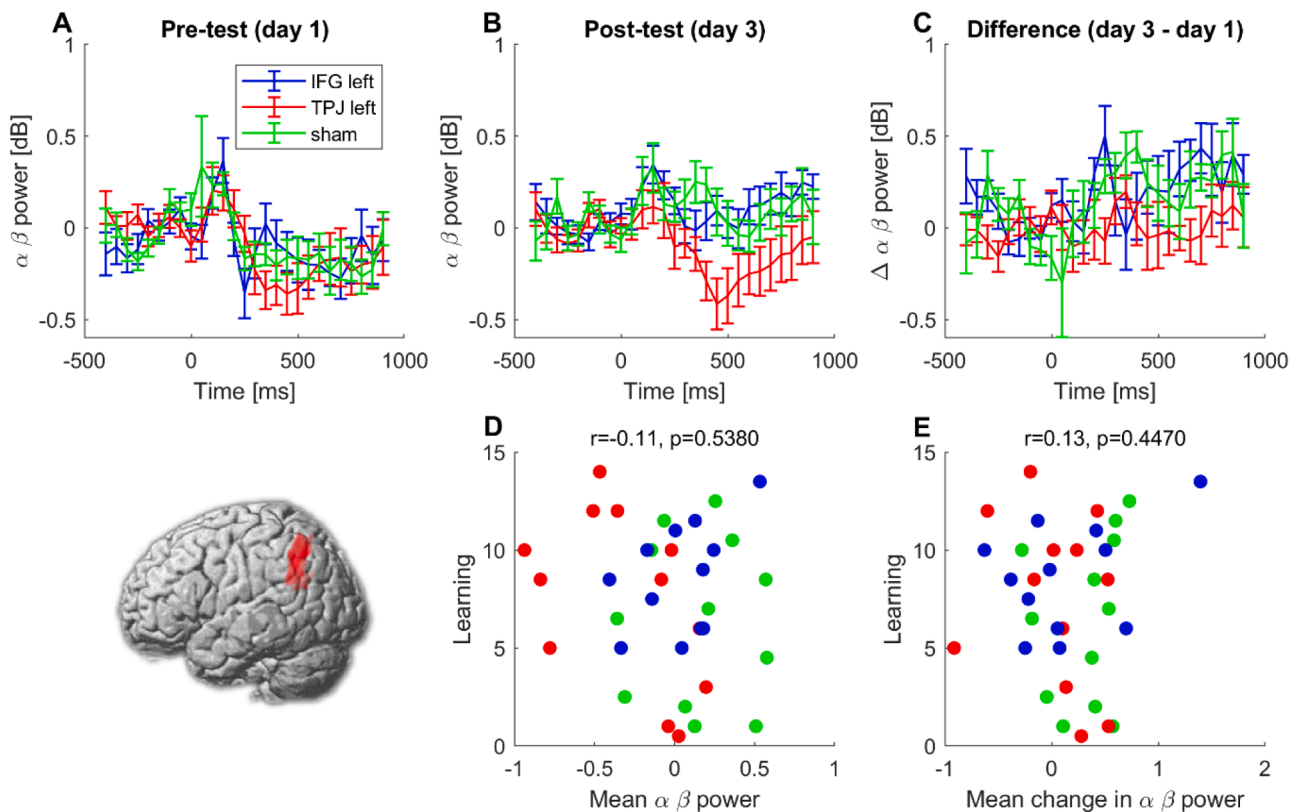

Fig. 4. Local activation at left TPJ (red part on 3D brain image at lower left) and impact on learning. Alpha and beta power decrease from baseline (indicating local activation) during noun naming at pre-test (A) and post-test (B), and difference from pre- to post-test in terms of stimulation condition (C). Local activation can be seen in all conditions at pre-test, but only in the TPJ stimulation condition at post-test. Time course is shown as mean ± standard error of mean. D. Absence of correlation between TPJ activation at post-test and learning in noun naming. E. Absence of correlation between the change in TPJ activation from pre- to post-test and noun learning.

after noun stimuli, but at none of the other ROIs or after verb stimuli (p>0.23). Thus, stimulation of the left TPJ tended to influence the change in activation of the stimulated area during noun naming from pre- to post-test. As event-related alpha and beta power showed similar effects, the two bands were then combined and the mean power at both bands at the left TPJ during noun naming was subjected to further analysis. As shown in Fig. 4, during the pre-test, there was a main effect of time ($F_{26,971}=4.2$, p<0.0001) indicating activation from baseline, but no main effect of stimulation condition (p=0.8) and no interaction between time and condition (p=0.3), indicating that participants were comparable across stimulation conditions at pretest. At the posttest on day 3, we still observed a main effect of time ($F_{26,971}=2.6$, p<0.0001), but now also an interaction ($F_{52,971}=1.6$, p=0.006), indicating that the

stimulation condition influenced the activation level at posttest. Pairwise comparisons revealed that this was due to a stronger activation after stimulation of the left TPJ than after left IFG and sham stimulation (p<0.05), suggesting that tDCS led to a stronger activation of the stimulated area at the posttest, as hypothesized. When investigating the difference between pre- and posttest, we observed a main effect of time ($F_{26,971}=2.1$, p=0.001), and a trend for interaction with stimulation condition ($F_{52,971}=1.3$, p=0.07).

However, the enhanced activation level during noun naming did not correlate with improved noun learning (Fig. 4, p>0.19), thus suggesting that the neural effect of tDCS did not translate to better learning.
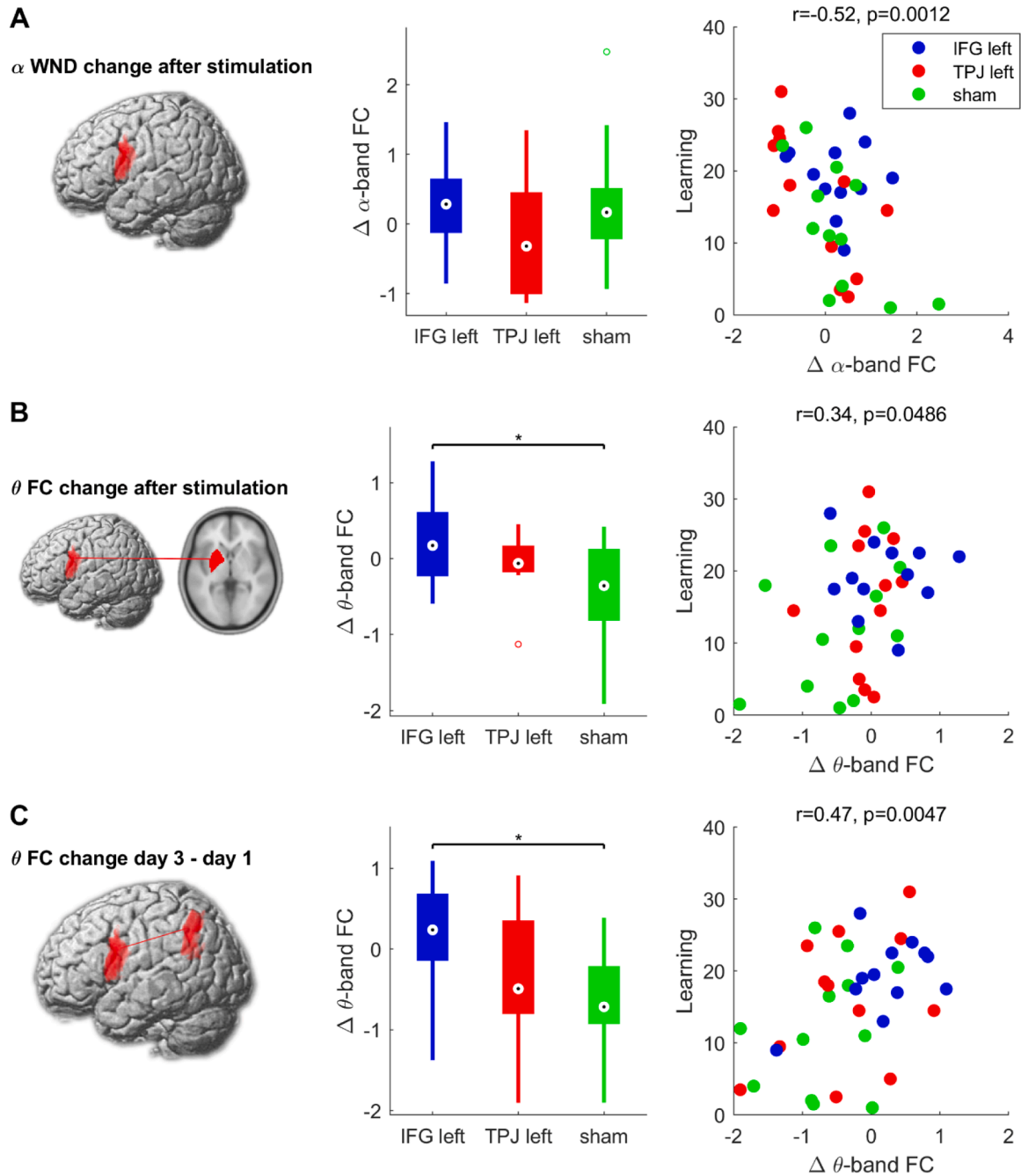

Fig. 5. Network correlates of improved new-word learning under tDCS. First column shows regions of interest, second column the comparison between stimulation conditions, third column the correlation with learning. A. Short-term change in global alpha-band FC between left IFG and rest of the brain. B. Short-term change in theta-band FC between left IFG and TPJ areas. C. Long-term change in theta-band FC between left IFG and TPJ.

3.3. Network interactions at rest

Next, we assessed the short-term change in resting-state FC from before to immediately after training and stimulation on day 2. There was no significant difference between stimulation conditions in the change of WND, i.e., global FC with the entire cortex, at any ROI or frequency band (p>0.16, 5 % FDR corrected). However, when considering all participants, a reduction in alpha-band WND at the left IFG correlated with better new word learning of verbs and nouns (r = -0.52, p = 0.0012, uncorrected, p=0.014, 5 % FDR corrected), as shown in Fig. 5A. No correlation with new word learning was found for alpha-band WND at left TPJ or the lentiform nucleus (p>0.9, 5 % FDR corrected), nor at any ROI in the other frequencies (p>0.24, 5 % FDR corrected).

When specifically considering FC of left IFG to the other ROIs, we observed a significant difference between the stimulation conditions in the change of theta-band FC with the lentiform nucleus ($F_{2,35}$ = 3.8, p = 0.034, uncorrected, Fig. 5B middle). A Tukey-Kramer HSD post-hoc test revealed that IFG stimulation enabled greater gains in FC than sham stimulation (p<0.05). Importantly, this increase in theta-band FC between IFG and lentiform nucleus correlated with better new-word learning of verbs and nouns (r = 0.34, p = 0.0486, uncorrected, Fig. 5B right).

Finally, we assessed long-term changes in resting-state FC from the recording before the pretest on day 1 to the recording after the post-test on day 3. There was no significant difference in WND between stimulation conditions (p>0.37) nor a correlation with new word learning (p>0.58) at any ROI or frequency band. However, as shown in Fig. 5C, when specifically considering FC between left IFG and the two other ROIs, we observed a significant difference between stimulation conditions in theta-band FC between IFG and TPJ areas ($F_{2,35}$ = 4.4, p = 0.020, uncorrected), with IFG stimulation leading to a greater increase than sham stimulation (p<0.05, Tukey Kramer HSD). Moreover, this increase correlated with better verb and noun learning (r = 0.47, p = 0.0047, uncorrected, p=0.037, 5 % FDR corrected). The remaining ROI and frequency bands did not show significant differences between stimulation conditions (p>0.44, 5 % FDR corrected), and no significant correlations with new word learning (p>0.08, 5 % FDR corrected).

When considering local oscillatory power changes in resting-state recordings at the 3 ROIs, we did not observe significant differences between stimulation conditions at any frequency, neither on the short term on day 2 (p>0.75, 5 % FDR corrected), nor on the long-term from day 1 to day 3 (p>0.85, 5 % FDR corrected). There was also no correlation between power changes and new word learning (p>0.49, 5 % FDR corrected).

4. Discussion

This study investigated the effect of HD-tDCS over two key nodes of the language network on local activation and network interactions before and after a new-word learning task. As expected, anodal tDCS over the left TPJ led to greater activation of the stimulated area during naming and this effect lasted at least until the day after stimulation. However, when investigating the effect of anodal tDCS over the left IFG, we did not notice changes in the activation level of the stimulated area. Instead, tDCS led to an increase in network interactions. Surprisingly, only the network effect, but not the enhanced local activation, translated into better word learning. This emphasizes the need for neuromodulation approaches targeting network interactions.

Stimulation in this study was applied to the left IFG or the left TPJ. In a classical model, left IFG and TPJ are among the principal language areas, linked by the articulate fasciculus. Damage to this system particularly impacts language functions, whether in the production or in the comprehension of speech (Catani et al., 2005; Geschwind et al., 1968; Hula et al., 2020). Furthermore, the primordial role of the left posterior inferior prefrontal cortex in phonological encoding in word production was previously established (Moliadze et al., 2019; Sakreida

et al., 2019). The left IFG is also thought to be involved in the retrieval of verbs (Pisano and Marangolo, 2020). Thus, the left IFG is an interesting target area for enhancing phonological processing and verb naming (Fiori et al., 2013; Marangolo et al., 2013; Peristeri et al., 2020). A brain network including left TPJ seems to be involved in word production. In particular, left TPJ may be involved in noun retrieval (Fiori et al., 2013). In sum, the left IFG and TPJ are the primary neural targets in the context of language training and word retrieval.

Our behavioral results are partly consistent with our expectations and previous studies (Fiori et al., 2013; Marangolo et al., 2013; Peristeri et al., 2020). We observed better verb learning during left IFG stimulation than sham stimulation (Fig. 2) in accordance with previous studies (Fiori et al., 2019, 2013; Marangolo et al., 2013). However, left TPJ stimulation did not lead to a significant effect on noun learning, unlike in previous studies (Fiori et al., 2013). The EEG recordings performed in this study enable us to investigate the reasons behind the presence or absence of behavioral effects in our participants.

The usual goal of tDCS is to modulate the excitability or activation level of the stimulated area. Indeed, we observed that after anodal HD-tDCS of the left TPJ, the area exhibited greater activation (as indexed by alpha and beta power decrease) during the task than after left IFG or sham stimulation (Fig. 43B). As TPJ is involved in the processing of language meaning, naming (Bowyer et al., 2019; Dogil et al., 2002), verbal memory (Pirmoradi et al., 2016; Rivera-Urbina et al., 2019) and in retrieval of nouns (Fiori et al., 2013), we would expect that this neural effect would result in a behavioral advantage during learning. Participants indeed had a higher percentage of learned words (in particular nouns) during stimulation of the left TPJ, but there was a large variability across participants, hence the difference was not statistically significant in our limited sample. It is further noteworthy that increased activation did not correlate with better learning (Fig. 4DE). Taken together, we conclude that the increase of local activation induced by anodal tDCS brings, if any, only a variable behavioral advantage. More intense training with multiple stimulation sessions may have led to more robust effects, as suggested by a previous study on aphasic patients with five consecutive days of naming task and tDCS stimulation (Fiori et al., 2013). However, the behavioral advantage of local activation seems to be less robust than changes in network interaction.

In participants receiving anodal tDCS over the left IFG, we did not observe modulation of local activation. Instead, the stimulation induced an enhancement of network interactions of the stimulated area with other areas implicated in learning and naming. This in turn enabled a robust and significant gain in verb learning. There is also evidence from previous studies that network interactions between language areas facilitate language processing (Bastiaansen et al., 2005). The network effects induced by tDCS associated with learning were observed in the theta frequency band. An increase in theta-band FC in the left temporo-parietal areas could reflect general memory processing demands (Röhm et al., 2001) and the retrieval of lexical semantic properties (Bastiaansen et al., 2005). HD-tDCS could facilitate the extent of network interaction and thereby help with memory coordination relating to language processing (Cao and Liu, 2018). Thus, enhancing theta-band FC appears to be an interesting target for enhancing learning capacities. Furthermore, we observed that a reduction of global alpha-band FC between the left IFG and the rest of the brain correlated with word acquisition, which reproduces findings of a previous study (Huang et al., 2022). Network interactions are furthermore also important for non-verbal learning. For instance, changes in network interactions were previously observed in correlation with visuo-motor skill learning (Manuel et al., 2018).

Previous research has shown that neural processing of nouns and verbs may differ. Verb processing is linked with activations of the left inferior frontal and bilateral middle temporal circuit, while noun processing activates the left inferior-mid temporal locus (Cappelletti et al., 2008; Faroqi-Shah et al., 2018; Shapiro et al., 2006). Moreover, brain stimulation acts differently on noun and verb learning, depending on the

stimulation site (Fiori et al., 2019, 2018, 2013; Marangolo et al., 2013; Pisano and Marangolo, 2020). Our analysis of the neural correlates of learning revealed both differences as well as similarities in the processing of verbs and nouns. We observed a significant modulation of the activation level at the left TPJ only during processing of nouns, but not during verbs. This may be indicative of the specific involvement of this brain region in noun processing. However, since these results were not correlated with better learning, we cannot confirm a causal link between left TPJ activation and improved noun processing. Stimulation of the left IFG enhanced learning of verbs while the effect on noun learning was not significant. This may again be interpreted as evidence for specific verb processing in this area. The FC enhancement between left IFG and left TPJ induced by HD-tDCS correlated with learning of both nouns and verbs (Fig. 4C). Both areas belong to higher-order language and memory processing networks which may support processing of both word types.

It is interesting to note that tDCS induces either local effects or network effects, depending on the stimulated area. We could speculate that the effect depends on the activation level of the stimulated area during the task. If an area shows spontaneous activation during the task, as the left TPJ, this activation can be enhanced with tDCS. Conversely, tDCS over areas with little spontaneous activation during the task, as the left IFG in our case, leads to an enhancement of interactions with those areas that do show an activation.

4.1. Limitations

Our study is limited by a small number of participants. In particular our exploration of the interaction between tDCS and training intensity needs to be interpreted with caution. Moreover, the spatial resolution of EEG source analyses is limited, especially for deeper brain regions such as the lentiform nucleus. The ability of EEG to localize signals coming from subcortical areas is therefore debated (Andersen et al., 2020; Attal and Schwartz, 2013; Krishnaswamy et al., 2017). Comparisons between surface EEG reconstructions and intracranial recordings have confirmed that source estimation based on high-density scalp EEG correctly localizes the current source of electrical activity in deep structures (Fahimi Hnazaee et al., 2020; Lucas et al., 2024; Nahum et al., 2011), thus giving credence to our results. Nevertheless, the role of the lentiform nucleus for language learning should additionally be investigated with other methods. Additionally, it is important to note that neural correlates may differ between neurotypical individuals and aphasia patients. It is thus necessary to confirm our findings in larger patient populations. These studies will need to include longer-term follow-up assessments and determine how factors such as lesion location, the type of aphasia, and time after onset influence the neural and behavioral response to stimulation. This will then contribute to a deeper understanding of the potential of HD-tDCS as a therapeutic tool for aphasia.

5. Conclusions

The main finding of this study is that a modulation of network interactions was associated with significant facilitation of learning, while the modulation of local activation was not. Similar advantages of network-wide processing over local processing have been previously shown for behavioral performance in visual and motor tasks (Allaman et al., 2020b) and for learning (Klug et al., 2022). We speculate that network interactions as indexed by FC may allow for a more efficient processing of task demands, thereby enabling particularly high performance. Thus, neuromodulation techniques targeting network interactions rather than local excitability may produce stronger and more robust behavioral effects. Indeed, several techniques have been suggested for modulating FC, e.g., based on transcranial alternating current stimulation (tACS) (Polanía et al., 2012) or neurofeedback (Mottaz et al., 2018; Scharnowski and Weiskopf, 2015). The present study suggests a further approach that can be tested in future work: induce activation of one area behaviorally with a suitable task, and activation of

another area with anodal HD-tDCS. If the observations of this study can be confirmed, this approach enhances the FC between the two regions in a behaviorally relevant manner.

While our results encourage future studies to explore the clinical utility of HD-tDCS and its network effects, it is essential to acknowledge that the observed effect is specific to verb learning. Thereby, tDCS stimulation protocols will need to be adapted to the type and severity of each patient's aphasia. Specifically targeting the needs of each patient could make it possible to determine the appropriate location and setup of stimulation for each aphasia disorder. This will require monitoring neural and behavioral effects. Our findings support the usefulness of EEG to monitor neural effects.

Data and code availability statement

The code of open access Matlab toolbox «NUTMEG» used for the analyses is available at: https://www.nitrc.org/projects/nutmeg/

Data will be made available upon request after publication.

Informed consent

Participants signed the consent form at their arrival at the laboratory, and before any study-related procedure.

CRediT authorship contribution statement

Camille Farcy: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Investigation, Formal analysis, Conceptualization. **Lea A.S. Chauvigné:** Methodology, Conceptualization. **Marina Laganaro:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Marion Corre:** Writing – review & editing. **Radek Ptak:** Writing – review & editing, Methodology. **Adrian G. Guggisberg:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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