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ORIGINAL ARTICLE

Anodal transcranial direct current stimulation sustainably increases EEG alpha activity in patients with schizophrenia

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Abstract

Aims: Transcranial direct current stimulation (tDCS) applied to the prefrontal cortex has been frequently used to elicit behavioral changes in patients with schizophrenia. However, the interaction between prefrontal tDCS and electrophysiological changes remains largely uncharted. The present study aimed to investigate cortical electrophysiological changes induced by tDCS in frontal areas by means of repeated electroencephalography (EEG) in patients with schizophrenia.

Methods: In total, 20 patients with schizophrenia received 13 minutes of anodal tDCS (1 mA) applied to the left dorsolateral prefrontal cortex (DLPFC). Repeated resting EEG was recorded before (once) and following (at five follow-up time-bins) tDCS to trace post-tDCS effects. We used sLORETA for source reconstruction to preserve the localization of brain signals with a low variance and to analyze frequency changes.

Results: We observed significant changes after the stimulation in areas highly connected with the stimulated DLPFC areas. The alpha 1 (8.5-10.0 Hz) activity showed a highly significant, long-lasting, increase for up to 1 hour after the stimulation in the postcentral gyrus (Brodmann area 2, 3, and 40). Significant yet unstable changes were also seen in the alpha-2 frequency band precentral at 10 minutes, in the beta-1 frequency band occipital at 20 minutes, and in the beta-3 frequency band temporal at 40 minutes.

Conclusion: We were able to show that anodal tDCS can induce stable EEG changes in patients with schizophrenia. The results underline the potential of tDCS to induce long-lasting neurophysiological changes in patients with schizophrenia showing the possibility to induce brain excitability changes in this population.

KEYWORDS
electroencephalography, neurophysiology, schizophrenia, transcranial direct current stimulation, treatment outcome

Appropriate fields The findings obtained from this research support a submission of this manuscript to the field of clinical neurophysiology and neuropsychology. Due to the method of investigation, a submission in the field of neuroimaging seems appropriate.

1 | INTRODUCTION

Transcranial direct current stimulation (tDCS) has been shown to be a potential treatment option for core symptoms of schizophrenia such as hallucinations or cognitive deficits. Several studies using tDCS in schizophrenia patients reported beneficial effects of anodal stimulation over the dorsolateral prefrontal cortex (DLPFC) by improving working memory performance[1,2] or reducing negative symptom severity.[3,4] While therapeutic effects of tDCS have been demonstrated in several studies, the electrophysiological changes following tDCS in this group, are mainly unclear. This study aims to shed some light on these post-stimulation processes. We aim at investigating how tDCS applied over the DLPFC modulates electrical brain activity in patients with schizophrenia, how it changes over time, and to what extend induced after-effects would last long term.

The constant flow of the direct current stimulation, applied by two electrodes placed on the scalp, is assumed to shift the neuronal resting membrane potential toward depolarization or hyperpolarization, depending on the direction of current flow.[5] Anodal stimulation is expected to result in an inward flow of current (relative to the cortical surface) leading to depolarization of pyramidal neurons, resulting in increases of cortical excitability on the stimulated and in interconnected brain areas.[6] Cathodal stimulation has been shown to induce hyperpolarization and thus decreases in excitability on site of stimulation and in interconnected areas.[7]

These long-lasting excitability changes following tDCS are assumed to stem from altered neuroplasticity and have been related to long-term potentiation (LTP) and long-term depression (LTD) like plasticity changes.[8] The underlying physiological processes are mainly mediated by activation of N-methyl-D-aspartate (NMDA) receptors and alterations of influx of calcium ions (Ca^{2+}) into the postsynaptic neurons. Whilst low rates of Ca^{2+} influx are viewed to support LTD, high rates of Ca^{2+} influx have been related to LTP-like plasticity.[9]

Electroencephalography (EEG) is a suitable tool to identify cortical electrophysiological changes induced by tDCS. Two types of recording methods are possible. First, online EEG, recorded during the application of tDCS, shows the immediate effects of stimulation but comprises some challenges and unwanted effects such as bridging between electrodes, noise, or artifacts which overlap the recorded neuronal changes.[10] Second, offline EEG, recorded before and after tDCS, can display pre/post changes between the unstimulated and stimulated brain but adheres no interference between the direct current and electrophysiological alterations of the brain.[10]

The established electrophysiological effects following tDCS are mainly based on studies in healthy subjects and suggest increased power in unspecific frequency bands after anodal stimulation over the DLPFC or the motor cortex. The affected frequency band seems to vary and depend on the stimulation protocol used and the (cognitive) tasks performed during stimulation. Whether these findings and the underlying concepts are applicable for schizophrenia patients remains unclear. So far, to our knowledge, only one study addressed electrophysiological changes in the EEG after tDCS over the DLPFC in schizophrenia patients. Here, only a three channel EEG was used as an additional assessment and only during cognitive tasks.[11] While the authors described an increased gamma power in the 2 mA condition after 40 minutes and a decrease gamma power in the sham condition after 40 minutes, the generalizability of these findings remains uncertain.

In this context, further research is needed to elucidate in what way tDCS applied to the DLPFC modulates brain activity in schizophrenia. Additionally, since prefrontal tDCS appears to have an impact on core symptoms in schizophrenia, resting-state EEG and source analysis techniques may help to better understand post-stimulation effects induced by tDCS. Thus, our goal was to identify the long-term neurophysiological changes following anodal tDCS applied to the left DLPFC in schizophrenia patients. By using baseline and repeated post-stimulation EEG measurements we expected resting-state EEG changes in the stimulated cortical and interconnected areas. Following the results of Hoy, Bailey[11] we expected changes in the gamma band. Second, based on these and findings in tDCS experiments on healthy participants, we proposed that these after-effects would be stable over a longer period of 1 hour.

2 | METHODS AND MATERIALS

2.1 | Participants

In total, 20 participants (seven women, thirteen men, mean age = 35.6 years, SD = 10.6) with an ICD-10 diagnosis of schizophrenia were recruited from the inpatient setting of the Psychiatric Hospital of the Ludwig-Maximilians-University Munich, Germany. Our study was approved by the local ethics committee and conducted according to the Declaration of Helsinki. Written informed consent was obtained from each volunteer prior to participation. Participants with neurological diseases, epilepsy, brain lesions or unstable psychopathology were not included. Furthermore, patients with a history of active substance abuse other than nicotine were not included. Demographic and clinical data were collected as part of the study. The symptom severity was measured as a part of this study using the Positive and Negative Syndrome Scale (PANSS),[12] the Global Assessment of Functioning (GAF),[13] and the Clinical Global Impression Scale (CGI).[14]

2.2 | EEG recording

The EEGs were recorded using a 32-channel Acti-Cap System (BrainProducts, Gilching, Germany) with electrodes arranged in an extended 10-20 system.[15] Each of the 6 EEG recordings lasted 6 minutes. The skin electrode impedance was kept below 5 kΩ. Electrodes were referenced to the average reference computed as the mean of all electrodes. With a sampling rate of 500 Hz the signals were digitalized using the BrainAmp amplifier (BrainProducts, Gilching, Germany). Visual block reaction was performed before and

during the recording of the EEG to ensure the quality of the recorded data. During the EEG recordings the participants were supervised by an investigator.

2.3 | tDCS

The direct current stimulation was performed using an Eldith DC-Stimulator Plus (Neuroconn, Ilmenau, Germany). Two sponges (7 cm × 5 cm; 35 cm^2), each soaked with 15-20 ml of NaCl, were used to cover the electrodes and to ensure low resistance during the stimulation. Using rubber bands, they were restrained on the target areas. The stimulated areas were determined using the EEG 10-20 system to ensure reliable results. The center of the anode electrode was located over the left dorsolateral prefrontal cortex (EEG position F3) with the short side of the electrode pointing to the EEG position CZ. The center of the cathode electrode was placed over the right supraorbital region (EEG position FP2) with the short side of the electrode pointing toward the EEG position CZ. The DC stimulation lasted 13 minutes using a voltage of 1 mA with a fade-in and fade-out of 15 seconds. The used stimulation protocol has become a safe[16] scientific standard procedure for anodal stimulation.[17]

2.4 | Procedure

Prior to the stimulation, a resting-state baseline EEG (6 minutes) was recorded. To position the DC electrodes the EEG cap was not removed but stayed in place during the DC stimulation to guarantee a constant electrode position. It was carefully lifted in the relevant areas and care was taken not to get the EEG cap wet to prevent bridging effects. Five resting-state post-tDCS EEGs (each 6 minutes long) were recorded starting every 10 minutes (see Figure 1). In total, the neurophysiological changes were monitored for everyone for close to 1 hour. During EEG recordings and tDCS, the participants sat on a comfortable chair in our laboratory where we kept all environmental influences such as light and noise as stable as possible. They were asked not to move or speak, to keep their eyes closed during stimulation and recordings but to remain in an alerted state.

2.5 | Data analysis

2.5.1 | Brain vision analyzer

Offline EEG analysis was performed using the Brain Vision Analyzer 2.0 software (BrainProducts, Gilching, Germany). Filters were applied to obtain a frequency range from 1 to 70 Hz (time constant 0.159 seconds 12 dB/oct, notch filter at 50 Hz). Visual inspection was used to remove artifacts. The artifact-free EEGs were segmented into 2 seconds intervals for further analysis. At least 120 artifact-free segments for each participant and measurement were available for further evaluation.

2.6 | Statistical analysis

For the statistical analysis, the following frequency bands were defined: delta (1.5-6.0 Hz), theta (6.5-8.0 Hz), alpha 1 (8.5-10.0 Hz), alpha 2 (10.5-12.0 Hz), beta 1 (12.5-18.0 Hz), beta 2 (18.5-21.0 Hz), and beta 3 (21.5-30.0 Hz). In a first approach to compare the different measurements, the median power $[(\mu V/m^2)^2/Hz]$ for each frequency band across all subjects was calculated for each EEG measurement (see Figure 2). For each frequency band, the median power of each measurement was compared with the baseline median power using the non-parametric Wilcoxon test. Bonferroni correction was used to control the occurrence of false positives.

2.7 | sLORETA

In a further step, we used the sLORETA software package[18] to more precisely locate changes in brain activity between different measurements in the aforementioned frequency bands. On a dense grid of 6239 voxels at 5 mm resolution sLORETA estimates, the current source density distribution for epochs of brain electrical activity throughout the brain volume. By assuming that neighboring neurons are simultaneously, and synchronously activated, sLORETA finds a solution for the three-dimensional distribution of the EEG signal. This assumption is based on data from single cell recordings in the brain showing strong synchronization of adjacent neurons.[19] The

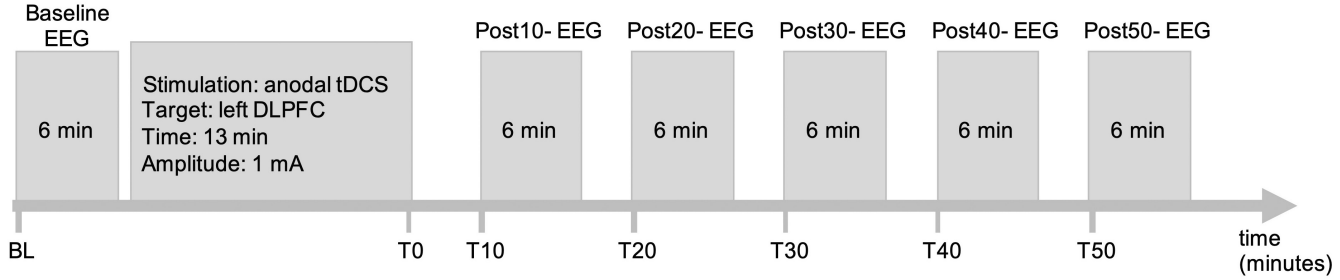

FIGURE 1 Sequence of resting-state EEG measurements and the DC stimulation. Following the baseline EEG, tDCS was applied with the anode placed over the left DLPFC and the cathode over the right supraorbital region. The post-stimulation resting-state EEGs were recorded in intervals of 10 min each lasting 6 min. Electrophysiological changes could be observed for almost up to 1 hour

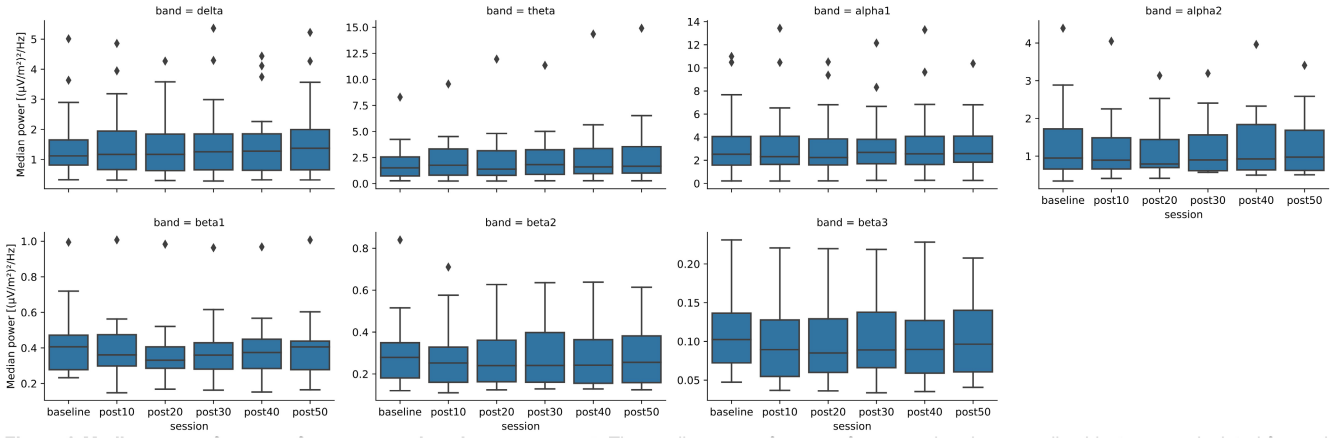

FIGURE 2 Median power for every frequency and each measurement. The median power for every frequency band across all subjects was calculated for each measurement. The boxplots show the median power, the interquartile range, the minimum, maximum, and outliers. Using the Wilcoxon test the statistical analysis revealed a significant difference in the beta 1 frequency band (see Table 2). After 20 min, the median power differed significantly from the baseline beta 1 median power

TABLE 1 Participants—demographic and clinical data

	Total	M	SD
Participants	20		
Sex (female:male)	7:13		
Handedness (right:left)	20:0		
Smoker (yes:no)	12:8		
Fagerström points (for Smokers)	12	4.6	2.5
Demographics			
Age (years)		35.6	10.6
School years		10.7	1.9
Age of onset (years)		24.4	6.0
Duration of illness (years)		11.2	8.1
CPZ equivalents		471.3	350.0
Clinical data			
CGI		4.7	0.6
GAF		60.0	7.6
PANSS positive		20.4	3.6
PANSS negative		29.4	6.5
PANSS general		42.8	7.5
PANSS total		92.6	14.4

Abbreviations: CGI, Clinical Global Impression; CPZ, chlorpromazine equivalent; GAF, Global Assessment of Functioning; *M*, mean; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

goal is to select the smoothest three-dimensional current distribution, which is a common procedure in signal processing,[20] to obtain a three-dimensional tomography that preserves the localization of brain signals with a low variance.[21] The resulting images represent the electrical activity of each voxel in the neuroanatomic MNI space as an amplitude of the computed current source density ($\mu A/mm^2$).

Using the statistical non-parametric mapping tool (SnPM) provided by sLORETA, some more specific statistical comparisons were performed. The tool uses the SnPM methodology known as Fisher's permutation test.[22] Holmes' non-parametric correction procedure for multiple comparisons[23] is integrated and the statistical analysis does not require any assumption of Gaussianity.[24] We used the "*t*-statistic on Log transformed data" test, with 5000 randomizations and a variance smoothing parameter of 0. This allowed us to do voxel-wise paired comparisons and to calculate the "Log *t*-test" thresholds corresponding to statistically significant thresholds $P < 0.05$ and $P < 0.01$.[25] In total, five comparisons were made between the post-stimulation EEGs and the baseline EEG.

Descriptive data analyses were performed using SPSS 25 Statistics.[26]

3 | RESULTS

3.1 | Descriptive

The participants showed high scores in the PANSS total score (M = 92.6 SD = 14.4), particularly on the PANSS negative scale (M = 29.5 SD = 6.5), characterizing our sample as markedly ill with a high level of negative symptoms. The GAF (M = 60.0 SD = 7.6) and CGI (M = 4.7 SD = 0.6) scores also point to markedly to moderate ill participants with moderate difficulties in social an occupational functioning. Detailed descriptive are displayed in Table 1. Further data about the intake of antipsychotic medication are shown in the supplement (Table S1).

3.2 | Power changes in frequency bands

The frequency power comparisons between the different measurements using the nonparametric Wilcoxon test revealed a significant difference in the beta 1 frequency power 20 minutes after the tDCS stimulation. This was the only visible change in frequency power, and it was only visible at this timepoint and vanished in the following measurements. All Bonferroni corrected P-values of this analysis can be seen in Table 2.

3.3 | Power changes in frequency bands using sLORETA

A long-lasting increase in the alpha 1 EEG spectral power predominantly in the Brodmann areas (BA) 2, 3, and 40 was the most prominent stimulation effect in the more specific sLORETA analysis. This significant increase was stable throughout the whole experiment. In the first measurement, 10 minutes after the stimulation, the increase was significant: Post 10 $t(19) = 6.52$, $P < 0.001$. Moreover, this effect continued to be significant in the second measurement, 20 minutes after the stimulation (Post 20 $t(19) = 5.65$, $P < 0.01$), 30 minutes after tDCS (Post 30 $t(19) = 5.49$, $P < 0.01$) and 40 minutes after the intervention (Post 40 $t(19) = 6.94$, $P < 0.01$). In the last measurement, 50 minutes after tDCS, the increase in the alpha 1 frequency statistically slightly decreased but was still significant: Post 50 $t(19) = 5.56$, $P < 0.05$.

In summary, for the alpha 1 power spectra, a single anodal tDCS applied to the DLPFC results in an increase in up to 1 hour. The changes in the alpha 1 power band are displayed in Table 3. Figure 3 shows the sLORETA images with XYZ (Montreal Neurological Institute [MNI]) coordinates for the changes in the alpha 1 band. The graphics displaying the significant changes in other frequency bands are detailed in the supplement (Figure S1).

Other frequencies showed isolated significant changes compared with the baseline EEG. A significant increase in alpha 2 power 10 minutes after the stimulation could be observed in the BA 4 (Post 10 $t(19) = 4.81$, $P < 0.05$) showing significant changes on the opposite hemisphere of the anodal stimulation. This increase was only visible directly after tDCS and could not be seen in the following measurements. A reduced beta power (12.5-30.0 Hz) was visible 20 and 40 minutes after the stimulation. These isolated reductions were only visible in two measurements and occurred in alternating brain regions. After 20 minutes, the beta 1 (12.5-18.0 Hz) power was significantly reduced in BA 18 (Post 20 $t(19) = -4.78$, $P < 0.05$) underlining the significant effect shown in the comparisons of the median power. This beta 1 change vanished and a significant reduction in beta 3 (21.5-30.0 Hz) power showed up 40 minutes after the anodal stimulation in BA 22 (Post 40 $t(19) = -4.88$, $P < 0.05$). These three singular frequency band changes could only be detected in individual measurements and did not match the changes in the alpha 1 power in statistical strength.

TABLE 2 Bonferroni-adjusted P-values for the comparisons between the different measurements and the baseline EEG. Using the Wilcoxon test the median powers of each frequency band were compared

	Post10	Post20	Post30	Post40	Post50
Delta	>0.999	>0.999	>0.999	>0.999	>0.999
Theta	0.220	>0.999	0.715	0.053	0.086
Alpha 1	>0.999	>0.999	>0.999	>0.999	>0.999
Alpha 2	0.348	0.825	0.570	>0.999	>0.999
Beta 1	>0.999	0.024	0.664	0.266	>0.999
Beta 2	>0.999	0.527	>0.999	>0.999	>0.999
Beta 3	0.615	0.448	0.768	0.242	>0.999

Abbrevations: Post 10 = median power of the EEG recorded 10 min after tDCS vs. median power of the baseline EEG.

4 | DISCUSSION

To the best of our knowledge, this is the first study using repeated resting-state EEG recordings to investigate long-term effects of anodal direct current stimulation applied to the left DLPFC in patients with schizophrenia. The most prominent and stable changes occurred in frontal areas more specifically in the anodal stimulated hemisphere, in the postcentral gyrus. The alpha 1 frequency band showed a significant, long-lasting increase that was visible in each measurement and thus lasted up to almost 1 hour after the stimulation. It was located primarily in BA 2, BA 3, and BA 40. Besides this increase in alpha 1 frequency, single frequencies showed significant, short-term changes at various time points. The alpha 2 power increased in BA 4, 10 minutes after the stimulation, the beta 1 shortly decreased in occipital areas (BA 18) 20 minutes after the stimulation and the beta 3 showed a short, significant decrease after 40 minutes in BA 22. These results underline the value of tDCS in influencing cortical brain areas and eliciting targeted changes.

In particular, the alpha 1 power in the somatosensory areas most likely shows in its spatial stability and statistical significance an aftereffect of tDCS. In its time stability, we assume that it

TABLE 3 Comparisons between current source density values of post-tDCS EEGs vs. baseline EEG using sLORETA. Displayed are the significant changes in the alpha 1 frequency band

	Region	XYZ (MNI)			Brodmann area	*t*-log-value
(a) Post 10	Postcentral Gyrus	−50	−25	35	2	6.52**
		50	−30	35		6.23**
		−45	−30	35		6.16**
		−55	−25	35		6.01**
		−50	−30	40		5.88**
		−50	−25	30		5.70**
		−55	−30	40		5.69**
		−45	−30	40		5.58**
		−60	−25	35		5.52**
		−55	−25	45		5.51**
	Postcentral Gyrus	−50	−20	40	3	6.07**
		−55	−25	40		6.05**
		−45	−25	40		6.02**
		−45	−20	40		5.97**
		−55	−20	40		5.80**
		−60	−25	40		5.68**
	Inferior Parietal Lobule	−55	−30	35	40	5.83**
		−45	−30	30		5.66**
		−50	−30	30		5.63**
	Precentral Gyrus	−50	−15	40	4	5.53**
(b) Post 20	Postcentral Gyrus	−55	−25	35	2	5.65**
		−50	−25	35		5.57**
(c) Post 30	Postcentral Gyrus	−50	−25	35	2	5.49**
		−50	−25	30		5.48**
(d) Post 40	Inferior Parietal Lobule	−45	−30	30	40	6.94**
		−50	−30	30		6.88**
		−55	−30	35		5.95**
		−55	−30	30		5.86**
	Postcentral Gyrus	−50	−25	35	2	6.86**
		−50	−25	30		6.62**
		−50	−30	35		6.40**
		−45	−30	35		6.13**
		−55	−25	35		5.94**
	Postcentral Gyrus	−45	−20	40	3	6.14**
		−50	−20	40		6.02**
		−45	−25	40		5.98**
(e) Post 50	Postcentral Gyrus	−50	−25	30	2	5.56*
		−50	−25	35		5.35*

Note: only the *t*-log-values of $P < 0.01$ or the most significant changes are shown.

Abbreviations: MNI, Montreal Neurological Institute; Post 10 = EEG recorded 10 min after tDCS vs. Baseline EEG.

*P-value < 0.05.

**P-value < 0.01.

reflects more than sensory perceptions or random changes and follows our assumption of time stable change due to stimulation. Unexpected was the occurrence of this change, not at the stimulated site, the DLPFC, but in motor areas. This can be explained by the well-known connection between the DLPFC and strongly interconnected motor and somatosensory areas.[27] This connection has been shown by evoking changes in motor areas through a stimulation of the dorsolateral prefrontal areas.[28] Although there

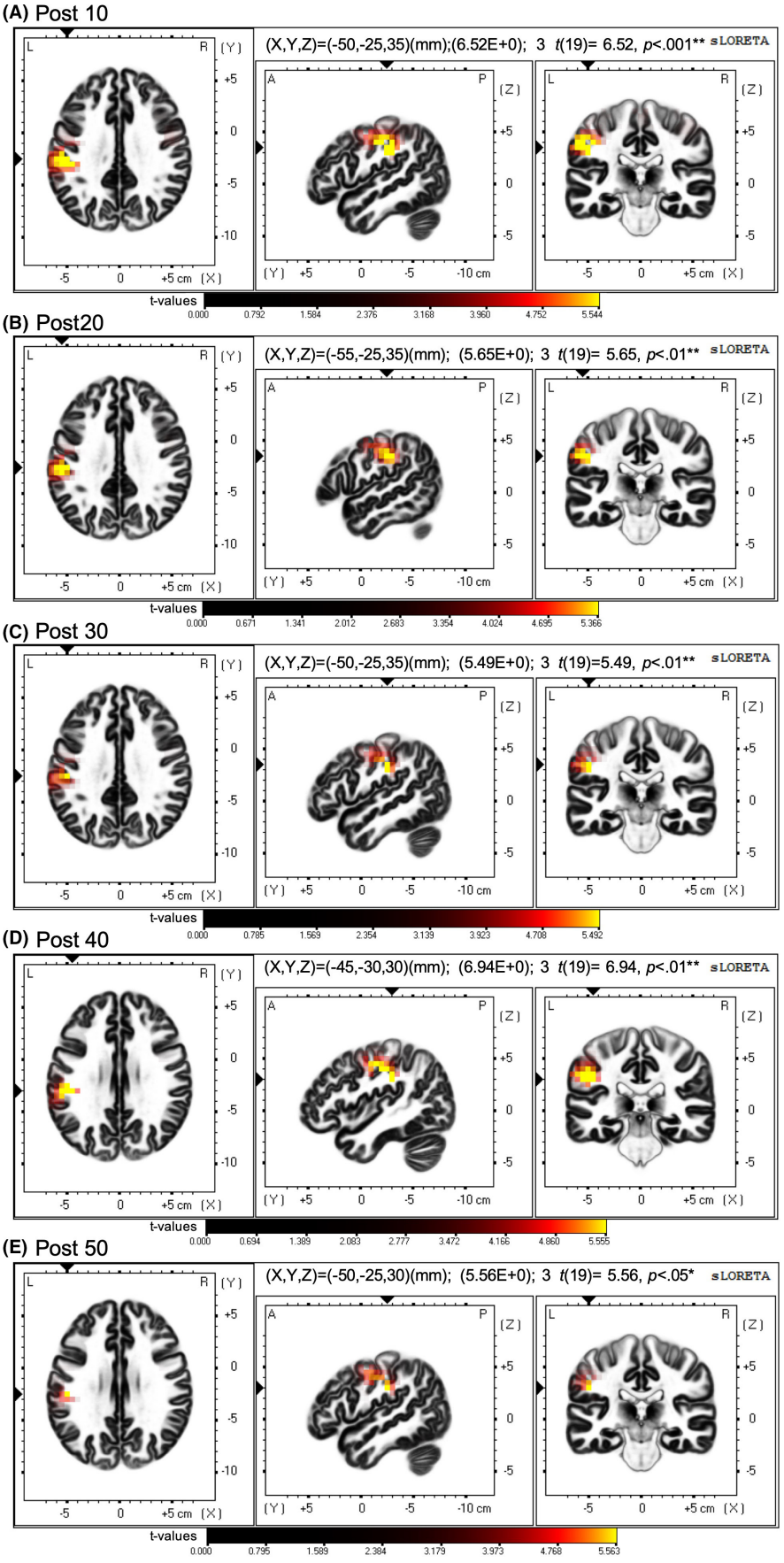

FIGURE 3 Power changes after the stimulation in the alpha 1 band. The stimulation effects on the mean current source density analyzed by LORETA. Changes are displayed as the difference between the post-stimulation EEGs (A) Post 10 min, (B) Post 20 min, (C) Post 30 min, (D) Post 40 min, (E) Post 50 min, and the baseline EEG. The most prominent, stable, and significant changes can be seen in alpha 1 power as an increase of activity in the Brodmann areas 2 and 40. Few indistinct and unstable changes can as well be seen in other bands and in altering timeframes (see Figure S1)

is no direct anatomical connection, there appears to be a relevant functional connection between the dorsolateral prefrontal and motor areas. This connection can explain the increased power visible in the sensorimotor cortex in our group of patients evoked by anodal tDCS applied to the DLPFC.

The significant increase in the alpha 1 band after the anodal stimulation of the DLPFC is not consistent with the gamma power changes observed by Hoy, Bailey[11] but in line with studies in healthy subjects using no tasks during tDCS and reporting an increased activity in the alpha band after DC stimulation.[29–31] Some results suggest that stimulation effects depend on the state of the brain during stimulation.[32–34] We assume that by synchronization, electrophysiological changes expand and stabilize themselves. Since the alpha activity is known to rise during resting-state episodes of the brain with eyes closed[35] and to reflects an relaxed state in the brain[36] the increase in alpha 1 activity can be attributed to the resting-state the brain was in during stimulation. Following this assumption, the different results between Hoy et al.[11] and our data also become apparent. While the EEGs and tDCS in our protocol were performed during resting states, Hoy et al. performed simultaneous working memory tasks known to be related to increased gamma power. By this assumption, tDCS could be used specifically to evoke and stabilize certain changes induced during the stimulation.

On a physiological level, the changes in the alpha 1 band can be seen as an expression of the ongoing neurophysiological changes after the stimulation. Alpha activity is determined by the activity of Ca^{2+} channels and can be modulated by the activity of these channels.[37,38] As tDCS is known to work through hyper−/ depolarization and thereby influencing the Ca^{2+} channels,[5,39] the alpha 1 power increase can be seen as the physiological aftereffect of the stimulation. Thus, the here observed effects can be interpreted as a plasticity and remote plasticity inducing effect of anodal tDCS in schizophrenia patients.

Not only the reductions in beta power after 20 and 40 minutes but also the increase in alpha 2 power after 10 minutes are considerably behind the changes in alpha 1 power in their statistical significance and consistency. Whether the changes were caused by the anodal stimulation, possibly by the physiological active cathode (placed over the right supraorbital region), or only spontaneous effects due to reduced concentration or due to constant relaxation cannot be finally clarified.

A limitation of this study is that we did not show these effects in comparison with a group of healthy controls or placebo stimulation. Therefore, no between-group or condition analysis was possible. We decided to conduct a strict within-subject effect as the detection of between-subject differences using this EEG approach with such sample sizes compromises several biases. Our pilot study aimed at testing such an approach in schizophrenia patients. Thus, it cannot be determined with absolute certainty if the increase in alpha power is connected to tDCS stimulation of the DLPFC in schizophrenia or if the increase shows a common aftereffect of tDCS stimulation. An increase in the alpha frequency band was also shown in other studies using different stimulation protocols, for example, Boonstra, Nikolin.[30] Furthermore, the role of somatosensory perceptions in the increase in alpha power as a side effect cannot be determined with complete certainty due to the missing placebo stimulation. The mechanisms leading to specific neurophysiological effects and the links with behavioral changes need to be investigated in further studies to use tDCS specifically and symptomatically.

Moreover, the positioning of the electrodes may have resulted in a stimulation of two brain regions. In addition to the anodal tDCS of the left DLPFC, the cathodal electrode was placed over the right supraorbital region, thereby applying cathodal tDCS to the right frontopolar cortex. Although we did not see any frequency changes in these or highly connected regions, an effect of the cathodal stimulation cannot be ruled out.

In addition, we used the sLORETA software package to calculate the location of the intracortical electrical activity measured at the surface of the head. Although it is a proven tool that has been validated in many studies, simultaneously active sources can only be separated if their fields are similarly strong and distinct enough. Weaker or deeper changes induced by tDCS may not be visible or could be masked by the strong changes in the alpha 1 frequency band.

In conclusion, we showed in a sufficient large cohort that frequency changes can be induced in schizophrenia patients, even though these patients usually show reduced alpha activity.[40] Furthermore, a single session of tDCS could induce solid significant changes over all times of measurement and thus up to almost 1 hour. This could be shown for the first time in patients with schizophrenia and underlines the therapeutic value of tDCS in psychiatric disorders. Following these results tDCS can be used to treat the reduced alpha activity in schizophrenia patients which is furthermore associated with negative symptoms.[41] In further studies, the physiological effect shown here should be further investigated in connection with behavioral outcomes, in contrast with healthy controls and in larger samples to underline the promising effects shown in this study.

AUTHOR CONTRIBUTIONS

BP wrote the final draft of the manuscript and was responsible for data analysis and literature search. AH, WS, and IP were responsible for data analysis, study design, and manuscript editing. DK, JH, and DG were contributing to results interpretation and data analysis. MS was responsible for data collection and participated in the data analysis. FP and PF contributed to the editing of the manuscript.

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CONFLICT OF INTEREST

Benjamin Pross, Irina Papazova, Duygu Güler, Jan Häckert, Daniel Keeser, and Melina Siamouli report no conflicts of interest. Wolfgang Strube received paid speakerships from Mag and More GmbH. Frank Padberg is a member of the European Scientific Advisory Board of Brainsway Inc., Jerusalem, Israel, and has received paid speakership from Mag and More GmbH and the neuroCare Group.

Peter Falkai was honorary speaker for Janssen-Cilag, AstraZeneca, Eli Lilly, Bristol Myers-Squibb, Lundbeck, Pfizer, Bayer Vital, SmithKline Beecham, Wyeth, and Essex. During the last 5 years, he was a member of the advisory boards of Janssen-Cilag, AstraZeneca, Eli Lilly, and Lundbeck. Presently, he is a member of the advisory boards of Richter Pharma, Abbot, and Otsuka.

Alkomiet Hasan received paid speakerships from Desitin, Janssen, Otsuka, and Lundbeck and was member of the Roche, Otsuka, Lundbeck, and Janssen Cilag advisory boards. He is publisher of the WFSBP and DGPPN guidelines for schizophrenia and member or the IFCN-guideline group for rTMS treatment.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request from the corresponding author. No informed consent was obtained to disclose the raw data; therefore, the data are not publicly available due to privacy restrictions.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

The protocol for this research project was approved by the local ethics committee and conducted according to the Declaration of Helsinki.

INFORMED CONSENT

Written informed consent was obtained from each volunteer prior to the participation.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

Not applicable.

ANIMAL STUDIES

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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