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List of abbreviations

BP:	Bipolar disorder
DLPFC:	Dorsolateral prefrontal cortex
EEG:	Electroencephalography
E-field:	Electric field
FDA:	Food and drug administration
GAF:	Global assessment of functioning
HC:	Healthy control
ICV:	Intracranial volume
tDCS:	Transcranial direct current stimulation
tES:	Transcranial electric stimulation
TMS:	Transcranial magnetic stimulation
MDD:	Major depressive disorder
MRI:	Magnetic resonance imaging
NTBS:	Non-invasive transcranial brain stimulation
OCD:	Obsessive-compulsive disorder
PANSS:	Positive and negative symptom scores
PFC:	Prefrontal cortex
ROI:	Region of interest
rTMS:	Repetitive transcranial magnetic stimulation
SCZ:	Schizophrenia

List of publications

Peer-reviewed Journal Articles

1. **Mizutani-Tiebel, Y., Takahashi, S., Karali, T., Mezger, E., Bulubas, L., Papazova, I., Dechantsreiter, E., Stoecklein, S., Papazov, B., Thielscher, A., Padberg, F. & Keeser, D. (2022). Differences in electric field strength between clinical and non-clinical populations induced by prefrontal tDCS: A cross-diagnostic, individual MRI-based modeling study.** ***NeuroImage: Clinical, 34,*** **103011.**
2. Mizutani-Tiebel, Y., Tik, M., Chang, K. Y., Padberg, F., Soldini, A., Wilkinson, Z., Voon, C. C., Bulubas, L., Windischberger, C. & Keeser, D. (2022). Concurrent TMS-fMRI: Technical Challenges, Developments, and Overview of Previous Studies. *Frontiers in Psychiatry*, *13*.
3. Padberg, F., Bulubas, L., Mizutani-Tiebel, Y., Burkhardt, G., Kranz, G. S., Koutsouleris, N., Kambeitz, J., Hasan, A., Takahashi, S., Keeser, D., Goerigk, S. & Brunoni, A. R. (2021). The intervention, the patient and the illness–Personalizing non-invasive brain stimulation in psychiatry. *Experimental Neurology*, *341*, 113713.
4. **Uenishi, S., Tamaki, A., Yamada, S., Yasuda, K., Ikeda, N., Mizutani-Tiebel, Y., Keeser, D., Padberg, F., Tsuji, T., Kimoto, S. & Takahashi, S. (2022). Computational modeling of electric fields for prefrontal tDCS across patients with schizophrenia and mood disorders.** ***Psychiatry Research: Neuroimaging, 326,*** **111547.**

Book Chapter

1. Chang, K. Y., Mizutani-Tiebel, Y., Soldini, A., Padberg, F., & Keeser, D. (2021). tDCS and Functional Connectivity. *Transcranial Direct Current Stimulation in Neuropsychiatric Disorders*, 159-172.

Conference Talks

1. Mizutani-Tiebel, Y., (2019). SIMNIBS simulations in schizophrenic, depressive patients and healthy subjects - how to better individualize neuromodulation. In the symposium of "Neuroimaging challenges to the field of Non-Invasive Transcranial Brain Stimulation (NTBS)"., Brain Stimulation and Imaging Meeting (BrainSTIM), Rome, Italy
2. Mizutani-Tiebel, Y., (2022). Investigating Theta Burst Stimulation Effects in Major Depressive Disorder with Concurrent TMS-fMRI. In the symposium of „Concurrent TMS-fMRI for Network Mapping and Proof of Neural Target Engagement"., International Federation of Clinical Neurophysiology (ICCN), Geneve, Switzerland

Conference Posters

1. Mizutani-Tiebel, Y., Takahashi, S., Karali, T., Dechantsreiter, E., Papazoya, I., Mezger, E., Bulubas, L., Stoecklein, S., Thielscher, A., Padberg, F., Keeser, D., (2020). Prefrontal tDCS e-field simulation with major depression and schizophrenia - Patient group difference and inter-rater / inter-individual variation. 7th International Conference on Non-invasive Brain Stimulation, Darmstadt, Germany (online)
2. Mizutani-Tiebel, Y., Chang, K. Y., Tik, M., Soldini, A., Bulubas, L., Dechantsreiter, E., Windischberger, C., Padberg, F., & Keeser, D. (2022). Concurrent TMS-fMRI – systematic review of methodological differences and sources of bias. Organization for Human Brain Mapping (OHBM), Glasgow, Scotland

Workshop / Lectures

1. Mizutani-Tiebel, Y., Chang, K. Y., (2021). TMS-fMRI experiences from Munich – from the sequence improvement to the first TBS applications in humans, Workshop "The combination of TMS/tDCS with MR Imaging", Ghent, Belgium
2. Keeser, D., Mizutani-Tiebel, Y., Papazov, P., (2022). Multimodal Neuroimaging. In Course P7: Neuro-Cognitive Methods III – fMRI. M.Sc. in Neuro-Cognitive Psychology, LMU Munich, Department of Psychology, Munich, Germany

Supervised Projects

1. Wilkinson, Z. D. (2021). Investigating the Immediate Effects of Intermittent Theta Burst Stimulation over the Prefrontal Cortex using Neuronavigation and functional Magnetic Resonance Imaging. In Module P8: Research Project. M.Sc. in Neuro-Cognitive Psychology, LMU Munich, Department of Psychology, Munich, Germany
2. Behnke, L. (2022). Transcranial Magnetic Stimulation simulated with SimNIBS 4.0 reveals electric field differences between DLPFC and M1. In Module P8: Research Project. M.Sc. in Neuro-Cognitive Psychology, LMU Munich, Department of Psychology, Munich, Germany

Contribution to the publications

1.1 Contribution to paper I

Paper I investigates the effect of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex (DLPFC) among major depressive disorder (MDD) patients, schizophrenia (SCZ) patients, and healthy controls (HC). I contributed to multiple stages through the realization of this paper. First of all, the conceptualization of the study design was done by me together with S.T., E.D., F.P. and D.K. From the pool of magnetic resonance imaging (MRI) scans collected by the co-authors E.M., L.B, I.P., S.S. and B.P., I selected the ones that meet our study criteria together with S.T.. I and S.T. consulted with A.T. and D.K. regarding the criteria of the MRI scans which are suitable for the electric field (e-field) calculation. The criteria I and S.T. checked were 1) the field of view includes the whole brain and the ears and there is no cut-off of the images 2) the subject is not wearing anything around the head such as electrodes or earphones, 3) there are no severe artifacts 4) the subjects match with age and gender among three subject groups. Once the subjects were selected, I ran a simulation of the tDCS-induced e-field together with S.T.. Both I and S.T. calculated the e-field of each subject (altogether 74 subjects) independently and blindly so that we can analyze the inter-rater reliability. The analyses of simulation results were analyzed and visualized by me together with D.K.. Afterward, I prepared the article and submitted it to the journal: “Neuroimage: Clinical”. Under the supervision of S.T., D.K. and F.P., I ran supplemental analyses and modified the article until its final publication. The first authorship is shared with the author S.T.. Preliminary analyses of this study were included in my master thesis submitted to LMU Munich, Department of Psychology for my degree of Master of Science in Neuro-Cognitive Psychology.

1.2 Contribution to paper II

Paper II is a replication analysis of paper I. The study was performed at Wakayama Medical University in Japan. I helped with the conceptualization of the study design with an independent set of Japanese subjects which replicated the subject groups recruited in Munich for paper I. The subject groups were MDD patients, SCZ patients and HC, as well as bipolar disorder (BP) patients which were added on top of the paper I conceptualization. The e-field calculation was run by the author S.U. and A.T. who followed the method which was established by myself and S.T. for paper I. After the first analysis results, I contributed to improving the analyses by adding more details, for example, to investigate the relationship between the e-field strength and the clinical characteristics such as Positive and Negative Symptom Scores (PANSS) and Global Assessment of Functioning (GAF) scores. After receiving the first draft of the article, I added more inputs in the introduction and the discussions by bringing in the newest study results related to our investigation. After all, the article was submitted to the journal "Psychiatry Research: Neuroimaging" by the first author S.U. and was successfully accepted.

2. Introduction

2.1 Theoretical background

2.1.1 Non-invasive transcranial brain stimulation

Non-invasive transcranial brain stimulation (NTBS) is a collective term that includes various kinds of brain stimulation techniques applied transcranially and non-invasively, eliminating the need for surgical procedures or anesthesia. This makes NTBS more accessible and less burdensome for patients compared to e.g. deep brain stimulation or electroconvulsive therapy. Among numerous kinds of NTBS being investigated recently, transcranial magnetic stimulation (TMS) and transcranial electric stimulation (tES) are the most extensively studied approaches. TMS operates by delivering electrical currents through a coil made of copper wires. It generates a magnetic field around the coil that can modulate brain activities. In contrast, tES utilizes electrodes placed on the scalp to deliver either direct current or alternating current. By applying these electrodes at different locations on the head surface with variant montages, a small current flowing through the skull modulates brain activity.

While both TMS and tES have been widely researched, the underlying physiological mechanisms of brain stimulations remain incompletely understood. The application of these stimulations can be modulated in many ways, e.g., stimulation strength, the rhythm of the stimulation, shape of the coil, montage of the electrodes, etc. Additionally, the role of the individual psychological, physiological and neurological factors in modulating stimulation effects is still unclear. Examples of such factors include arousal levels, hormonal states and neuronal morphology.

2.1.2 NTBS in the field of psychiatry

NTBS is an emerging method to treat psychiatric patients. The U.S. Food and Drug Administration (FDA) has approved a treatment method using repetitive TMS (rTMS) for pharmacotherapy-non-responsive MDD (Blumberger et al., 2018), obsessive-compulsive disorder (OCD) (Carmi et al., 2018) and smoking cessation (Zangen et al., 2021). Recent guidelines on the therapeutic usage of NTBS reported level A evidence for rTMS treatment with MDD as well as level B evidence for rTMS treatment with posttraumatic stress disorder (Lefaucheur et al., 2020) and tDCS treatment with MDD and addiction/craving (Lefaucheur et al., 2017).

While meta-analyses demonstrate the effectiveness of NTBS at the group level, non-responders remain a significant issue (Gaynes et al., 2014; Meron et al., 2015; Trevizol et al., 2016). The methodology of NTBS treatment leaves room for significant improvement to enhance the overall treatment result. Numerous studies have explored modifications of the treatment parameters in various ways to assess their effects on treatment outcome. These attempts lead to various suggestions for improved methods of NTBS, such as theta burst stimulation using TMS (Blumberger et al., 2018) or high-definition tDCS (Kuo et al., 2013). However, due to the incomplete understanding of the underlying physiological mechanisms of NTBS, these modifications are often applied empirically (i.e. by changing dosage, sequence, stimulation location etc.). Researchers aim to untangle the relationship among all factors that may affect the result of the NTBS treatment in order to individualize the treatment in the most effective way for each individual. Nonetheless, this journey takes a long time as clinical studies are time-intensive, often requiring several years to yield publishable results. Additionally, the large number of potential parameter modifications further complicates the systematic optimization.

2.1.3 Role of electric field modeling in the field of NTBS

E-field is a physical field generated by electrically charged properties in space. When NTBS is applied through the skull and reaches neurons in the brain, the neurons create e-fields and they propagate. The strength of the e-fields, which serves as a proxy for the "received dosage of the stimulation", can be measured through in-vivo electrophysiological recordings. Such recordings have been performed in epileptic patients undergoing brain surgery (Opitz et al., 2018; Wang et al., 2022). However, due to invasive nature of this approach, the number of subjects is limited.

To facilitate e-fields investigations, a computational modelling method has been developed (Huang et al., 2019; Thielscher et al., 2015). These computational modelling typically requires only structural MRI of individual subjects which can be obtained non-invasively within some minutes. By segmenting the MRI scan in each tissue type, it enables us to estimate the intensity and the propagation of the e-fields in the individual brain. E-field calculation enables the researchers to investigate the estimated stimulation effect of NTBS. Therefore, it provides an opportunity to promptly investigate the individual response to a certain parameter of NTBS and its association with other factors, such as demographics, diagnosis/symptoms and other neurological factors. Consequently, e-field modeling is expected to become a powerful and practical tool to individually modify NTBS treatment protocols prior to the initiation of therapeutic sessions.

2.2 Research Project

2.2.1 Research questions and goals

As discussed above, e-field calculation is an effective method to quickly investigate the estimated received dosage of the brain stimulation. The research question was whether

the e-field strength differs among different subject groups and if so, where in the cortex the difference lies and what it is associated with. In a string of three successive research projects conducted in Germany and Japan, we investigated tDCS- and TMS-induced e-fields with two independent subject groups of MDD, SCZ, HC as well as BP (only in Japanese cohort).

Typically, tDCS treatment for these patients is given at the intensity of 1 or 2 mA with the electrode montage defined by the international 10-20 Electroencephalography (EEG) system. However, such "one size fits all" approaches in the field of psychiatry have shown inhomogeneity in the treatment responses (Lefaucheur et al., 2017). Previous studies showed inter-individual variability in tDCS-induced motor response (Wiethoff et al., 2014) and cerebral blood flow response (Workman et al., 2020). tDCS-induced e-field studies have demonstrated inter-individual variability measured by both intracranial in-vivo method (Huang et al., 2017; Opitz et al., 2016) and computational modelling (Antonenko et al., 2021; Laakso et al., 2015). This series of research projects aim to visualize e-field variability induced by tDCS and TMS among different patient groups as well as individuals and investigate the association between the e-fields and various factors such as demographics as well as structural and functional factors.

2.2.2 Research Project 1 - tDCS with German Cohort (paper I)

Research project 1 was conducted at the Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Germany. T1-weighted structural MRI scans were collected from three groups: MDD (n = 25), SCZ (n = 24), and HC (n = 25). E-fields were simulated with a common tDCS MDD treatment protocol (i.e. 2 mA at F3 and -2 mA at F4 according to the international 10-20 EEG system). SimNIBS software (https://www.simnibs.de) (version 2.0.1.) was used to calculate the e-fields. Two

independent and blinded investigators calculated the e-fields following the same instructions.

The results were analyzed at the whole-brain level as well as at regions of interest (ROI) in the prefrontal cortex (PFC) subregions. We found that the e-fields at the whole brain level were reduced with MDD and SCZ compared to HC, but no difference between MDD and SCZ was observed. Following the voxel-wise analysis, reduced e-fields with SCZ compared to HC were consistently found by both investigators at the bilateral superior frontal gyrus and right middle frontal gyrus regions. The ROI analysis revealed that reduced e-fields intensities between MDD and HC as well as SCZ and HC are observed at Brodmann's areas 8B and 9 specifically. At the descriptive level, we generally observed considerable inter-individual variability of e-fields intensities within groups, especially at the higher percentile. Additionally, we observed that the Euclidean distance of electrode localization between investigators 1 and 2 was significant and this difference was correlated with the number of activated voxels between investigators 1 and 2 for MDD and SCZ at both F3 and F4.

These results from paper 1 suggest three important insights: 1) the dose-response relationship of NTBS cannot be simply translated from healthy individuals to clinical populations, 2) even within the same clinical groups, the stimulation parameters should be individually decided, 3) precise electrode positioning is important to reach a reliable treatment result. The result shows that e-fields calculation is an effective method to develop the individualized NTBS parameter before starting the treatment sessions.

2.2.3 Research Project 2 – tDCS with Japanese Cohort (paper II)

Following paper 1, a precision study was conducted at the department of neuropsychiatry, Wakayama Medical University in Japan. T1-weighted structural MRI scans were

analyzed from MDD (n=23), SCZ (n=23), HC (n=23) as well as BP patients (n=24). E-field was calculated by two independent and blinded investigators for each study following the same protocol as paper 1 using the SimNIBS software (version 2.1.1.).

Paper 2 found reduced e-field intensity observed at 99.5th percentile with MDD and SCZ compared to HC which replicates the study result of paper 1. There was no difference observed between BP and HC as well as among the patient groups. With the voxel-wise analysis, significantly reduced e-field was found with SCZ compared to HC in the bilateral frontal lobe, which supports the results from paper 1, as well as in the cerebellum and brain stem which was newly found. These differences were consistently observed by two investigators. Paper 2 investigated the correlation between the e-field intensities and the psychiatric symptoms or global functioning, measured as PANSS and GAF scores. However, no correlation was observed. The results from paper 2 support the overall findings from paper 1 and add some more important insights: 1) e-field correlation shown at cerebellum and brain stem 2) no correlation between e-fields and PANSS as well as GAF scores.

2.2.4 Research Project 3 – TMS with Japanese Cohort (not part of the thesis)

Following paper 2, we investigated the TMS-induced e-field intensity with the same Japanese dataset as paper 2 (MDD, SCZ, BP, HC) at left DLPFC with the stimulation intensity of $di/dt = 10^6$ A/s. Other procedures were kept the same as in paper 2. This TMS study found no significant difference in the e-field intensities among the subject groups which differs from the result with tDCS. However, reduced e-field was observed with male subjects compared to females. Additionally, the positive correlation between age and the e-field strength was observed mainly in the left parahippocampal area. Estimated intracranial volume (ICV) showed a significant negative correlation with the e-field

intensities in the right temporal lobe, bilateral occipital lobe and cerebellum, but only by one of the investigators. These results suggest that the e-field characteristics differ between tDCS and TMS. In the case of TMS treatment, anatomical information, such as ICV, associated with demographics, such as gender and age, might play important roles in order to individualize the treatment parameters.

2.3 Conclusion, limitation and future perspective

This series of three studies investigated e-fields intensities induced by tDCS and TMS with two independent cohorts from Germany and Japan. tDCS-induced e-fields were significantly reduced with MDD and SCZ compared to HC at higher percentiles, but we observed no difference between MDD and SCZ. This result was replicated by both cohorts. On the other hand, the analysis of TMS-induced e-fields showed no significant difference among subject groups. However, the e-fields strength was associated with gender, age and ICV either at the whole-brain level or at certain areas in the cortex.

Computational e-field modeling is a relatively simple method that could be implemented at every hospital which has an opportunity to obtain a structural MRI scan of the patients. The structural MRI scan takes ~10 minutes, and the e-field calculation takes ~5 minutes after pre-processing the MRI scan which can be automatically performed by some simple commands. E-field modeling provides us an opportunity to individualize the NTBS protocols (i.e. stimulation dosage and location) in a way that can most likely reach an individual's cortex with a higher intensity. As the e-field intensity is shown to associate with the tES functional outcome (Kasten et al., 2019), we can expect that the individualized NTBS protocol with higher e-fields leads to a better treatment outcome.

Computational modeling is simply calculated on the basis of the anatomical features of the individual head by assigning the conductivity to various segmentations of the head components such as skin, skull, grey matter and white matter. Even though e-field modelling has been validated with in-vivo electrophysiological recordings (Opitz et al., 2018; Wang et al., 2022), we should stay attentive to the fact that this is an approximation. In the real world of NTBS, the conductivity value may differ among individuals (Hoekema et al., 2003; McCann et al., 2019). Circadian rhythm and hormonal levels as well as the levels of fatigue, arousal, attention, anxiety, and excitement may potentially affect the outcome of NTBS (Krause & Cohen Kadosh, 2014). These factors cannot be simulated with the e-field modeling, but that is why I strongly suggest controlling other factors that can be simulated with the simple e-field modelling in order to improve the treatment results of NTBS in the field of psychiatry. As a future direction, it is important to investigate whether 1) e-field strength predicts the treatment outcome, and 2) individualizing the treatment protocol using e-field modeling improves the treatment outcome.

3. Summary

NTBS is a method to modulate brain activity by applying electric or magnetic stimulations non-invasively. A therapeutic NTBS has been used in the field of psychiatry to treat pharmacotherapy-resistant patients of e.g. MDD, SCZ and OCD. Although meta-analyses show the efficacy of NTBS treatment compared to sham stimulation, non-responders are extensively observed looking at the individual patient level. Therefore, there is a strong need for investigation into optimization or individualization methods of the stimulation protocol in order to suppress the number of non-responders.

This series of three studies investigated e-fields as one of the potential methods which can be used to individualize the stimulation. E-fields can be computationally modeled using an individual's structural MRI. E-fields reflect the received dosage of the stimulation and it is expected to be associated with the functional outcome of NTBS. These three studies investigated e-fields induced by tDCS and TMS with two independent cohorts of MDD, SCZ, HC (and BP in one of the cohorts). The aim of the studies was to examine whether: 1) e-fields differ among various subject groups 2) e-fields are associated with any external factors 3) inter-individual and inter-rater differences are observed.

The results show that the tDCS-induced e-fields are reduced with MDD and SCZ compared to HC, though MDD and SCZ did not show a significant difference. These differences were constantly observed in the prefrontal cortex. However, we also observed a considerable inter-individual difference in e-fields which reminds us of the importance of protocol individualization. When it comes to TMS-induced e-fields, the group difference and inter-individual difference were diminished. However, we observed gender and age effect associated with the e-fields intensities.

This series of studies demonstrated the usability of e-fields computational modelling in the field of therapeutic application of NTBS in psychiatry. Increasing the stimulation intensity, for example, according to the diagnosis, age and gender, can potentially optimize the stimulation protocol which may lead to a better outcome of NTBS treatment in the field of psychiatry.

4. Zusammenfassung

NTBS umfasst Methoden zur Modulation der Gehirnaktivität durch nicht-invasive elektrische oder magnetische Stimulation. Therapeutisch wird NTBS in der Psychiatrie zur Behandlung von therapieresistenten Patienten eingesetzt, z. B. bei MDD, SCZ und OCD. Obwohl Meta-Analysen die Wirksamkeit der NTBS-Behandlung im Vergleich zur Scheinstimulation belegen, spricht ein Teil der Patienten nicht auf die verfügbaren NTBS Protokolle an. Daher ist es dringend erforderlich, Methoden zur Optimierung oder Individualisierung der Stimulationsprotokolle zu untersuchen, um die Ansprechraten zu erhöhen.

Die in dieser Arbeit vorgestellten drei Studien untersuchten elektrische Feldstärken als eine Möglichkeit zur Individualisierung der Stimulation. Elektrische Felder können mit Hilfe des strukturellen MRTs einer Person rechnerisch modelliert werden. Elektrische Felder spiegeln dabei die empfangene Stimulationsdosis wider, und es wird erwartet, dass sie mit dem funktionellen Ergebnis bzw. therapeutischem Ansprechen von NTBS in Verbindung stehen. Die drei Studien untersuchten die durch tDCS und TMS induzierten elektrischen Felder bei zwei unabhängigen Kohorten von ProbandInnen mit MDD, SCZ, HC (und BP in einer Kohorte). Das Ziel der Studien war es, zu untersuchen, ob: 1) sich die elektrischen Felder zwischen den verschiedenen Probandinnengruppen unterscheiden 2) die elektrischen Felder mit externen Faktoren in Verbindung stehen 3) interindividuelle und Inter-Rater-Unterschiede zu beobachten sind

Die Ergebnisse zeigen, dass die tDCS-induzierten elektrischen Felder bei ProbandInnen mit MDD und SCZ im Vergleich zu HC reduziert sind, wobei ProbandInnen mit MDD und SCZ keinen signifikanten Unterschied zeigten. Diese Unterschiede wurden durchgehend im präfrontalen Kortex beobachtet. Wir beobachteten jedoch auch einen

beträchtlichen interindividuellen Unterschied bei den elektrischen Feldern, was die Bedeutung der individuellen Anpassung des Protokolls verdeutlicht. Bei den TMS-induzierten elektrischen Feldern waren die Gruppenunterschiede und die interindividuellen Unterschiede weniger ausgeprägt. Allerdings beobachteten wir einen geschlechts- und altersabhängigen Effekt im Zusammenhang mit der Intensität des elektrischen Feldes.

Diese Studienreihe zeigte die Eignung der rechnerischen Modellierung von elektrischen Feldern im Bereich der therapeutischen Anwendung von NTBS in der Psychiatrie. Eine Erhöhung der Stimulationsintensität, z. B. in Abhängigkeit von der Diagnose, dem Alter und dem Geschlecht, kann das Stimulationsprotokoll optimieren, was zu einem besseren Ergebnis der NTBS-Behandlung in der Psychiatrie führen kann.

5. Paper I

Mizutani-Tiebel, Y., Takahashi, S., Karali, T., Mezger, E., Bulubas, L., Papazova, I., Dechantsreiter, E., Stoecklein, S., Papazov, B., Thielscher, A., Padberg, F. & Keeser, D. (2022). Differences in electric field strength between clinical and non-clinical populations induced by prefrontal tDCS: A cross-diagnostic, individual MRI-based modeling study. *NeuroImage: Clinical*, *34*, 103011.

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Differences in electric field strength between clinical and non-clinical populations induced by prefrontal tDCS: A cross-diagnostic, individual MRI-based modeling study

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ABSTRACT

Introduction: Prefrontal cortex (PFC) regions are promising targets for therapeutic applications of non-invasive brain stimulation, e.g. transcranial direct current stimulation (tDCS), which has been proposed as a novel intervention for major depressive disorder (MDD) and negative symptoms of schizophrenia (SCZ). However, the effects of tDCS vary inter-individually, and dose–response relationships have not been established. Stimulation parameters are often tested in healthy subjects and transferred to clinical populations. The current study investigates the variability of individual MRI-based electric fields (*e-fields*) of standard bifrontal tDCS across individual subjects and diagnoses.

Method: The study included 74 subjects, i.e. 25 patients with MDD, 24 patients with SCZ, and 25 healthy controls (HC). Individual e-fields of a common tDCS protocol (i.e. 2 mA stimulation intensity, bifrontal anode-F3/cathode-F4 montage) were modeled by two investigators using SimNIBS (2.0.1) based on structural MRI scans.

Result: On a whole-brain level, the average e-field strength was significantly reduced in MDD and SCZ compared to HC, but MDD and SCZ did not differ significantly. Regions of interest (ROI) analysis for PFC subregions showed reduced e-fields in Sallet areas 8B and 9 for MDD and SCZ compared to HC, whereas there was again no difference between MDD and SCZ. Within groups, we generally observed high inter-individual variability of e-field intensities at a higher percentile of voxels.

Conclusion: MRI-based e-field modeling revealed significant differences in e-field strengths between clinical and non-clinical populations in addition to a general inter-individual variability. These findings support the notion that dose–response relationships for tDCS cannot be simply transferred from healthy to clinical cohorts and need to be individually established for clinical groups. In this respect, MRI-based e-field modeling may serve as a proxy for individualized dosing.

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1. Introduction

Transcranial direct current stimulation (tDCS) is a transcranial electrical stimulation (tES) and non-invasive brain stimulation (NIBS) technique, used as experimental and therapeutic interventions to modulate cortical activity. tDCS of the prefrontal cortex (PFC) showed initial evidence of efficacy in psychiatric disorders, e.g. in major depressive disorder (MDD) (Brunoni et al., 2016; Moffa et al., 2020) and negative symptoms of schizophrenia (SCZ) (Valiengo et al., 2020; Yu et al., 2020). Compared to other NIBS methods, such as repetitive transcranial magnetic stimulation (rTMS), tDCS is less expensive, portable, and potentially suitable for all treatment settings, including home treatment (Palm et al., 2018). In contrast to rTMS, however, standard tDCS protocols provide a non-focal, less targeted stimulation and no individual adjustment of stimulation intensity (Bikson et al., 2016). Current tDCS protocols usually apply fixed intensities (e.g. 1 or 2 mA) and standardized electrode montages (e.g. defined by the international 10–20 EEG system).

However, it is questionable whether such standardized protocols are optimal for tDCS. Inter-individual variability of tDCS effects in motor and non-motor regions has generally been reported with standardized "one size fits all" applications (Wiethoff et al., 2014; Workman et al., 2020). Furthermore, therapeutic applications of tDCS with psychiatric patients showed considerable inhomogeneity in the treatment response (Lefaucheur et al., 2020). Wörsching et al. (2017) observed that active tDCS induced additional variability in resting-state connectivity compared with sham tDCS. Recent studies show several factors that affect the behavioral outcome of tDCS, such as the baseline resting-state functional connectivity (FC) (Cerreta et al., 2020) and concentration of the neurochemicals (Filmer et al., 2019). However, the true picture of these inter-individual response variations is not fully understood yet.

To account for the inter-individual variability in response to tDCS interventions, personalization is suggested in terms of intensities and targets. tDCS-induced electric field (e-field) has been proposed as a proxy for individual adjustment of tDCS intensity as it reflects the received dosage of the stimulation. Recent intracranial field measurements (Huang et al., 2017; Opitz et al., 2016) and modeling studies (Antonenko et al., 2021a; Laakso et al., 2015) demonstrated variability in e-field intensity across subjects. Inter-individual variation in e-field strength has been partially explained by variable structural (Mosayebi-Samani et al., 2021) and functional neuroanatomy (López-Alonso et al., 2014; Wiethoff et al., 2014) but is not yet completely understood. Recent machine learning study proposed precision dosing of tDCS derived from individual e-field characteristics, which predicted the responders of cognitive training (working memory improvement) with 86% accuracy (Albizu et al., 2020). To individualize the tES intensity, reverse-calculation e-field modeling recently showed a promising result (Caulfield et al., 2020).

The variation in electrode positioning also contributes to tDCS-induced e-field variability. Opitz et al. (2018) investigated the e-field distribution with surgical epilepsy patients and recommended keeping the electrode positioning error under 1 cm to achieve the desired e-field distribution. Five percent of electrode mislocalization at F3/F4 and M1/SO (1–1.5 cm drift with average head size) lead to a significant difference in e-field distribution. A validation of motor cortex localization based on C3/C4 locations with international 10–20 EEG demonstrated a low to fair intraclass correlation coefficient (ICC) between two independent raters. These e-field intensity variations due to a less precise electrode localization may be a source of variability in tDCS response.

For computational modeling of e-fields, SimNIBS (https://www.simnibs.de) is an established approach based on Finite-Element Method (FEM) (Thielscher et al., 2015). This free software package allows researchers to simulate tDCS application on subjects' anatomical magnetic resonance imaging (MRI) scans. tDCS-induced e-fields are calculated by separating the different tissue types. SimNIBS stimulation simulation allows numerical statistical comparison of e-field strength, and it can visualize the e-fields distribution in the brain.

The present study investigates the variation of e-field strength and distribution for a standard protocol of prefrontal tDCS in MDD and SCZ, i.e. bifrontal anode-F3/cathode-F4 montage with 2 mA stimulation intensity (Bajbouj et al., 2018; Blumberger et al., 2012; Brunoni et al., 2013; Padberg et al., 2017) as left dorsolateral prefrontal cortex (DLPFC) plays an important role in the pathophysiology of MDD (Koenigs and Grafman, 2009) as well as negative symptoms of SCZ (Potkin et al., 2009). In order to imitate clinical practice, two blinded investigators placed the electrodes over F3 and F4 by calculating both positions based on nasion, inion, and mastoids coordinates. Thus, this study aims to characterize the cross-diagnostic and inter-individual variability of tDCS-induced e-fields and to test the assumption that dosage parameters can be readily transferred from non-clinical to clinical populations.

2. Method

2.1. Participants

All patients and HC were recruited in the Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Germany. Data from 74 right-handed subjects were analyzed in the study divided into three groups: MDD (n = 25, male = 10, age: 38.1 ± 10.2 yrs, range: 22–56 yrs), SCZ (n = 24, male = 11, age: 36.9 ± 13.4 yrs, range: 20–59 yrs), and HC (n = 25, male = 13, age: 35.5 ± 11.1 yrs, range: 20–57 yrs). All MDD subjects had a primary DSM-5 diagnosis of Major Depressive Disorder and HDRS-21 (Hamilton Depression Rating Scale) score of ≥ 15. SCZ subjects were diagnosed with ICD-10 F20. None of the subjects reported a history of neurological disorder and none of the HC group had a psychiatric disease. Three subject groups were matched for age and gender. The study was approved by the local ethics committee. The study was conducted in accordance with the code of ethics of the world medical association (declaration of Helsinki). All participants gave their written informed consent.

2.2. MRI data acquisition

All subjects underwent T1-weighted structural MRI using a 3-Tesla MR-scanner equipped with a 20-channel head coil (Magneton Skyra, Siemens Healthineers, Erlangen, Germany). The participants wore ear-plugs for noise protection. T1-weighted images were acquired with a 3D magnetization-prepared fast gradient echo (MPRAGE) sequence (TR: 1900 ms, TE: 2.2 ms, flip angle: 9°, 0.8 mm^3 isotropic voxels).

2.3. Electric field calculation

For MRI-based e-field modeling, we used SimNIBS (version 2.0.1; http://Simnibs.de/) (Thielscher et al., 2015); a free software that allows the calculation and simulation of the e-fields induced by tDCS or other NIBS. We applied SimNIBS in Ubuntu 16.04. environment. The respective software was required for the following SimNIBS procedure: FreeSurfer (version 6.0.0; https://surfer.nmr.mgh.harvard.edu/) (Dale et al., 1999; Fischl et al., 1999) and FMRIB Software Library (FSL) (version 6.0.0; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). Additionally, we used some open source tools such as MeshFix (Attene, 2010; Attene and Falcidieno, 2006) for meshing and Get DP (Dular et al., 1998) for FEM computation.

Before SimNIBS was started, "mri2mesh" was used to generate an individual tetrahedral volume mesh of the head (Windhoff et al., 2013). To model prefrontal tDCS, a standard bipolar montage was used; anodal-F3/cathodal-F4 montage according to the international 10–20 EEG system. The electrode size was set to a rectangular with dimensions of 4.5 cm × 6.5 cm. We simulated the thickness of the electrodes as 5 mm and the saline-soaked sponges with a thickness of 6 mm. The current intensity was set to 2 mA and −2mA on the left and right hemispheres respectively. Conductivity was set as default settings of SimNIBS (WM:

0.126 S/m, GM: 0.275 S/m, CSF: 1.654 S/m, Skull: 0.010 S/m and skin: 0.465 S/m).

The localization of the electrodes was performed to imitate the clinical practice where F3/F4 locations are determined by measuring the head size using the locations of inion, nasion, and mastoids. For modeling, a python script was used which was developed by the SimNIBS developers. This script automatically calculated F3 and F4 coordinates by inserting individual inion, nasion, and mastoids coordinates. The direction of the electrodes was manually adjusted so that the sponges are in parallel to each other.

SimNIBS calculation was conducted independently by two blinded investigators (i.e. investigators 1 and 2). The outcome of the individual e-field distribution map was visualized using gmsh (Geuzaine and Remacle, 2009; Schöberl, 1997). SimNIBS software calculates the peak values of the e-field intensity (E) as a ratio of voltage divided by distance (E = V/m) at the 50th, 75th, 90th, 95th, 99th, and 99.5th percentiles of the voxels. For example, when the e-field value is indicated at the 90th percentile, it means that 90 percent of the voxels have an e-field intensity lower than its shown value (Opitz et al., 2015).

2.4. Transformation to volumetric space

The individual electric fields calculated with the SimNIBS were converted to volumetric space using the script "msh2nifti" developed by Nicholas Cullen (University of Pennsylvania, Neuroscience graduate group 2018, https://github.com/ncullen93/mesh2nifti/blob/master/msh2nifti.py). We have made some minor changes, such as integrating an input and output folder structure to the script, which otherwise did not change the script's content. msh2nifti was used to transform the grey matter (GM) to volumetric space. The voxel size was set to 2 mm.

2.5. Analyses and visualization

2.5.1. Numerical statistical calculations

Numerical statistical calculations were performed using IBM SPSS Statistics (version 20.0.0.1, IBM Corp. Armonk, NY) and R Studio (version 1.2.5033, https://www.r-project.org/) (R Core Team, 2013). The Shapiro-Wilk test of normality showed that our e-field dataset is not normally distributed, therefore we used non-parametric statistical tests. Inter-rater reliability was tested using the ICC test. Kruskal-Wallis test and post-hoc Mann-Whitney test were applied to see the variance of electric field strength in SCZ, MDD, and HC. Age and gender were included as covariates. The significance level was Bonferroni corrected and set at 0.008 (0.05 divided by 6).

2.5.2. Voxel-based whole-brain analysis

Voxel-wise whole-brain analysis was conducted using FSL randomize v2.9. Age and gender were inserted as covariates. Family-wise error (FWE) rate was controlled and only FWE-corrected p values of <0.05 were accepted as significant results. To assign and extract the voxels with significant results and anatomical regions where the voxels were located, we used the command "autoaq" in FSL. Clusters with more than 30 voxels are reported. For the atlas, we used the Talairach Daemon Labels (Lancaster et al., 1997; Lancaster et al., 2000; Talairach, 1988). Results on volumetric space were further registered to surface space using workbench v1.3.2 with the command 'wb_command -volume-to-surface-mapping' (https://www.humanconnectome.org/software/workbench-command/-volume-to-surface-mapping) and projected onto the Conte69 surface template (Van Essen et al., 2011).

2.5.3. Voxel-based ROI analysis in PFC

Using the Sallet atlas (Sallet et al., 2013), we placed our regions of interest (ROI) in 6 regions: Brodmann's area (BA) 8B, 9, 9/46D, 9/46 V, 10 and 46. This selection was based on our secondary analysis of the Escitalopram versus Electrical Direct-Current Theror Depression Study (ELECT-TDCS; Brunoni et al. 2017) which showed an association of GM volume in PFC subregions and improvement of depression scores only after tDCS, but not after escitalopram or placebo (Bulubas et al., 2019). First, "fslstats" was used to extract non-zero voxels in the ROIs with binary masks. Based on these data, the maximum e-field within the ROIs was calculated and averaged across individuals in each ROI. The 50th and 75th percentile values of the averaged maximum e-fields were then used as the low-cut threshold. The number of voxels exceeding the threshold was calculated in each of the 6 ROIs for each threshold and investigator. Group differences between MDD, SCZ, and HC were calculated with the Kruskal-Wallis test and post hoc pairwise Wilcoxon test. The significance level was Bonferroni corrected.

3. Results

The demographic characteristics of all subjects are shown in Table 1. No significant difference was observed among subject groups regarding the age, gender, and intracranial volume (ICV) (age; Kruskal Wallis test; Chi-square = 0.793, p = 0.673, df = 2 / gender; one-way ANOVA; $F(2,71) = 0.976$, $p = 0.382$ / ICV; chi-square test; $X^2(2, N = 74) = 0.72$, $p = 0.696$). Fig. 1 illustrates the distribution of the e-field for the 75th and 99th percentile thresholds of the voxels for each subject group and rater. The e-field maximum was in PFC regions.

3.1. Numeric comparison of e-field strength between experimental groups and investigators

Using Kruskal Wallis tests, we observed a significant difference in electric field strength between MD, SCZ, and HC groups, which varied between both investigators. Investigator 1 observed a significant difference from the 75th percentile of the voxels and above, whereas investigator 2 observed a significant difference only above the 95th percentile. Significant differences were found between MDD and HC as well as SCZ and HC (post-hoc Mann-Whitney tests). However, the difference between MDD and SCZ did not reach significance at any percentile threshold (Fig. 2, Table 2).

3.2. Global voxel-wise spatial comparison in whole brain (Group and inter-rater comparison)

Fig. 3 shows the comparison of e-field intensities between the groups as well as between investigators. Table 3 gives an overview of all brain regions included in the clusters with more than 30 voxels (FWE-corrected $p < 0.05$). We observed no significant differences between investigators, although subject group analysis revealed discrepant findings. Consistent findings by both investigators were the differences in e-field intensity between SCZ and HC located in frontal lobe regions; SCZ showed a weaker e-field bilaterally for the superior frontal gyrus and in the right middle frontal gyrus. Other discrepant findings for both investigators are shown in Table 3.

Table 1
Demographic and clinical characteristics of the study sample.

	HC	MDD	SCZ
	(n = 25)	(n = 25)	(n = 24)
Age (range)	20–57	22–56	20–59
Age (mean ± SD)	35.5 ± 11.28	38.1 ± 10.46	36.9 ± 13.71
Male (%)	13 (52%)	10 (40%)	11 (46%)
ICV (cm^3 ± SD)	1558 ± 168	1558 ± 196	1623 ± 187
BDI	–	23.5 ± 10.27	–
MADRS	–	21.7 ± 6.97	–
PANSS (total)	–	–	54.8 ± 17.1

Abbreviations: HC = Healthy control, MDD = Major depressive disorder, SCZ = Schizophrenia, SD = Standard deviation, ICV = Intracranial volume, BDI = Beck's Depression Inventory, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale.

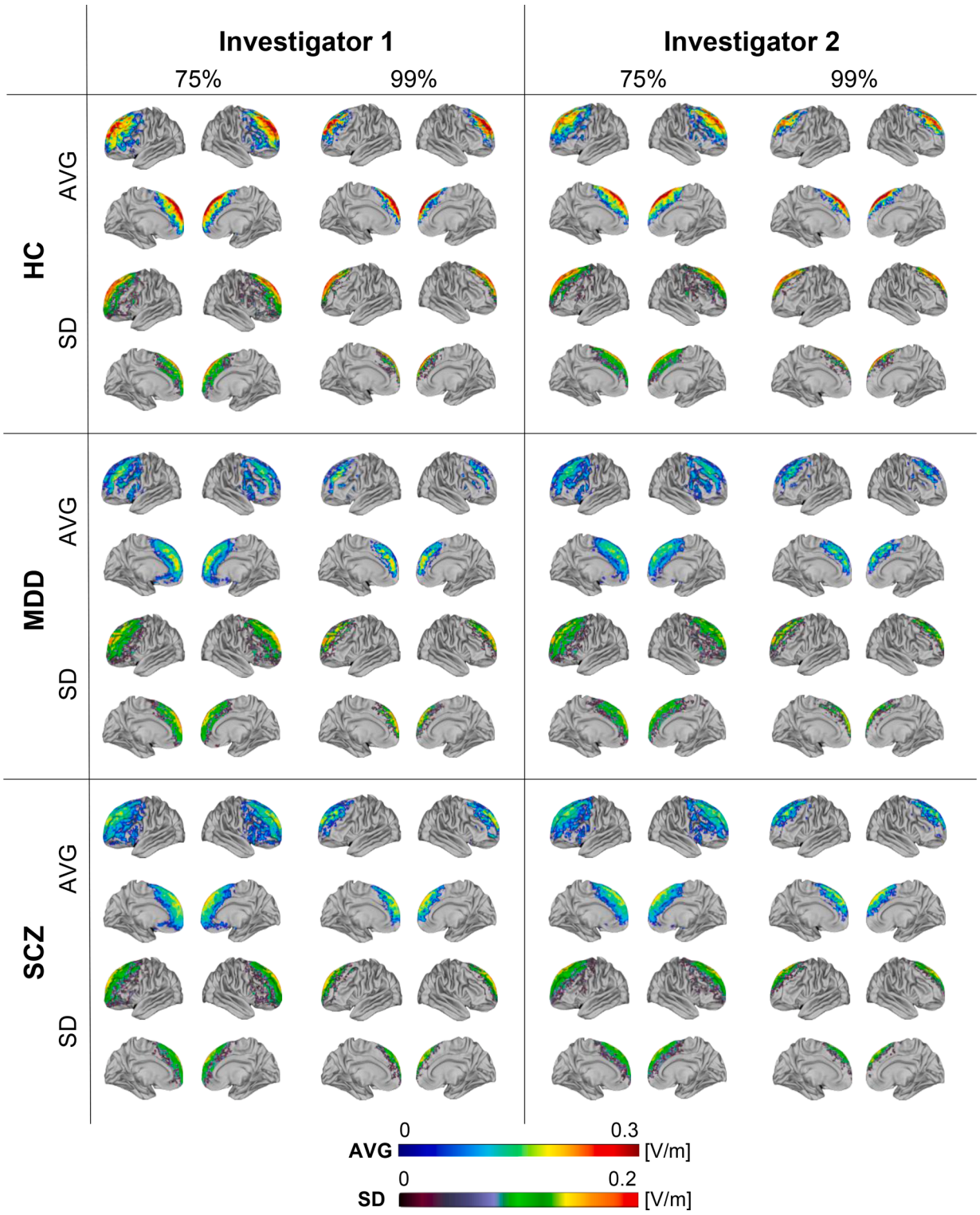

Fig. 1. Distribution of average (AVG) e-field strength and standard deviation (SD). AVG and SD of the e-field distribution are illustrated for three groups (HC: healthy control, MDD: major depressive disorder, SCZ: schizophrenia), two intensity thresholds (75th and 99th percentile of the voxels) and two investigators (1 and 2).

3.3. Local voxel-wise comparison in PFC regions

Fig. 4 depicts the group variability of e-fields across PFC regions according to Sallet parcellation (Sallet et al., 2013). The graph shows the number of voxels at each PFC region that had an e-field value higher than the 50th or 75th percentile thresholds of the averaged total PFC e-field value across all subjects. A significant difference between groups was consistently observed by both investigators for BA 8B, 9, and 9/46D. A difference between MDD and HC was detected for bilateral BA 8B, 9, and right BA 9/46D regions, at both 50th and 75th thresholds. The difference between SCZ and HC was observed for right BA 8B and left BA 9 regions, at the 50th percentile threshold. However, the effect was only found for the right BA 9 at the 75th percentile threshold.

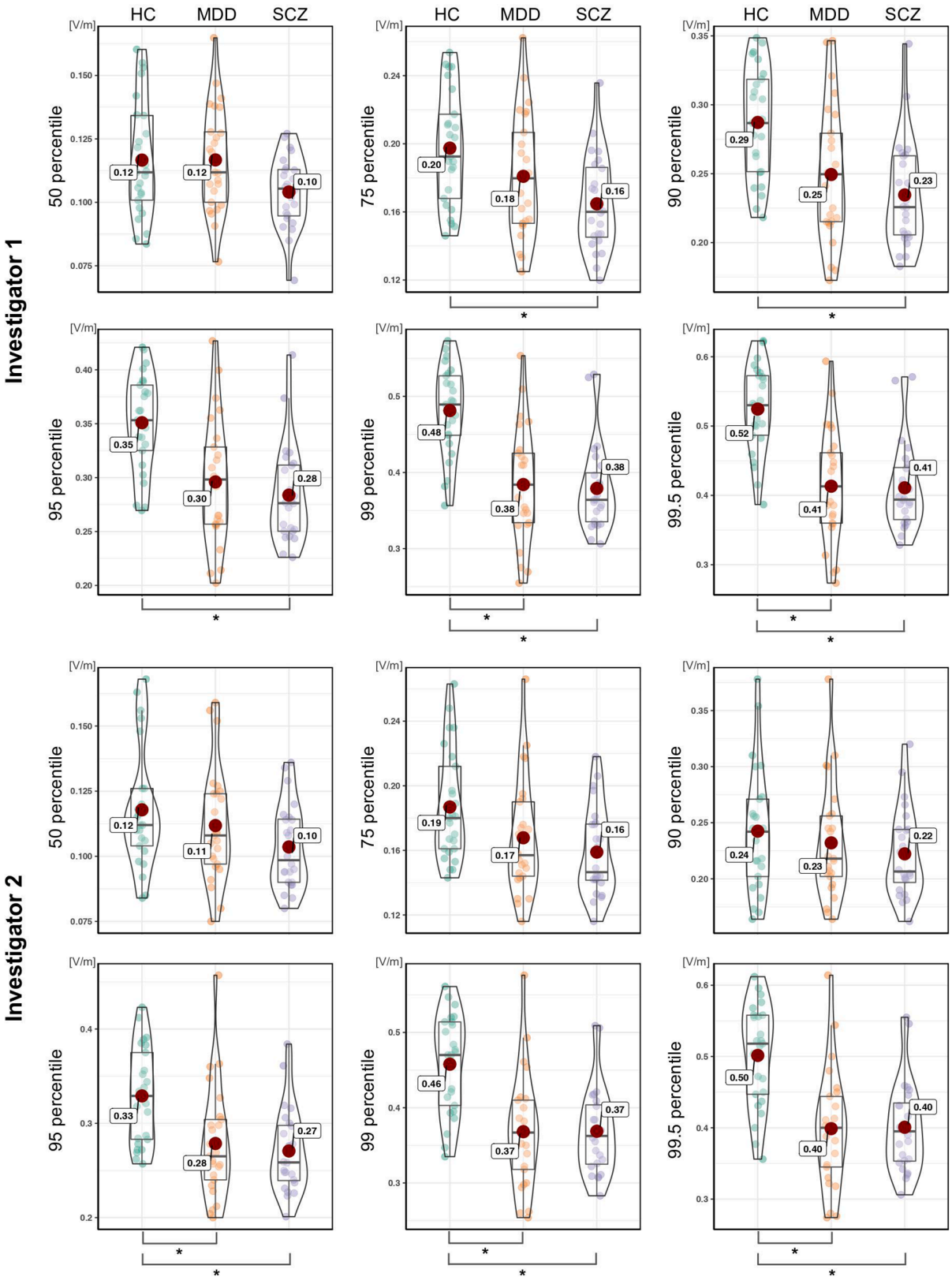

Fig. 2. Group comparison of e-field intensity for both investigators, The vertical axis shows the e-field strength (V/m). The horizontal axis is the three subject groups (HC = healthy controls, MDD = major depressive disorder, SCZ = schizophrenia) separated for six percentile thresholds of the voxels (50%, 75%, 90%, 95%, 99% and 99.5%). The dots in each graph indicate every individual's e-field value. * = $p < 0.008$ (0.05/6 - corrected for multiple comparison).

Table 2
Statistical results of the e-field strength subject group comparison.

Kruskal Wallis test												
	50%		75%		90%		95%		99%		99.5%	
	X^2	P	X^2	P	X^2	P	X^2	P	X^2	P	X^2	P
Investigator 1	–	–	10.53	< 0.005	16.06	< 0.001	20.57	< 0.001	26.44	< 0.001	27.77	< 0.001
Investigator 2	–	–	–	–	–	–	16.6	< 0.001	21.85	< 0.001	22.45	< 0.001
Post-hoc Mann–Whitney test												
MDD vs HC												
	50%		75%		90%		95%	99%		99.5%		
	U	P	U	P	U	P	U	P	U	P	U	P
Investigator 1	–	–	–	–	170	< 0.006	136	< 0.001	96	< 0.001	89	< 0.001
Investigator 2	–	–	–	–	–	–	145.5	< 0.001	111.5	< 0.001	108	< 0.001
SCZ vs HC												
	50%		75%		90%		95%	99%		99.5%		
	U	P	U	P	U	P	U	P	U	P	U	P
Investigator 1	–	–	136	< 0.001	105	< 0.001	88	< 0.001	68	< 0.001	63	< 0.001
Investigator 2	–	–	–	–	–	–	112.5	< 0.001	92	< 0.001	90	< 0.001

Abbreviations: HC = Healthy control, MDD = Major depressive disorder, SCZ = Schizophrenia.

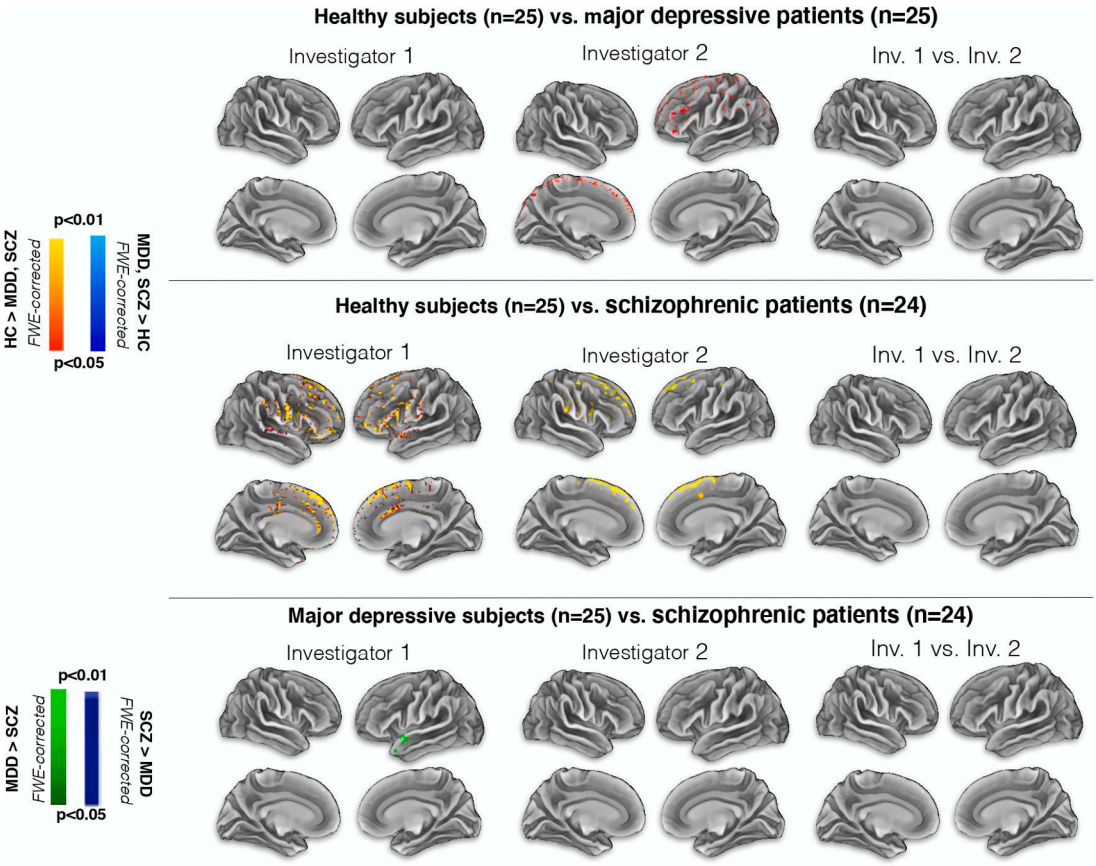

Fig. 3. Comparison of the electric field intensity using volumetric data projected onto the surface space. For investigator 1 there was a significant difference between HC and SCZ as well as MDD and SCZ. For investigator 2 there was a significant difference between HC and MDD as well as HC and SCZ. Though these results differ between investigators, we observed no statistically significant difference between investigators 1 and 2.

3.4. Inter-investigator difference

Intraclass correlation between both investigators was strong, except for the 90th percentile of the voxels, where a significant difference was observed between investigators in HC data at the 90th percentile ($p < 0.01$) (Fig. 5A). The calculation of the euclidean distance showed a significant difference for the electrode positions XYZ applied by the two investigators. This was evident with the F3 electrode for HC ($p < 0.01$) and SCZ ($p < 0.05$) for the XYZ coordinates, and MDD ($p < 0.05$) for Y and Z coordinates (Table S1). With the F4 electrode, there was a significant Euclidean difference for Y and Z coordinates with MDD ($p < 0.01$), SCZ ($p < 0.05$) and HC ($p < 0.01$). For the X-coordinate, there was

Table 3
Brain regions consisting the clusters.

Investigator 1										
						Main area in the cluster				
Direction of effect	Cluster	Number of voxels	X	Y	Z	Hemisphere	Lobe	Cortical area	GM/WM	Brodmann area
HC > SCZ	Cluster 1	20,210	−4	34	44	Right	Frontal	Superior Frontal Gyrus	WM	–
						Right	Frontal	Middle Frontal Gyrus	WM	–
						Left	Frontal	Superior Frontal Gyrus	WM	–
						Left	Frontal	Inferior Frontal Gyrus	WM	–
						Left	Frontal	Middle Frontal Gyrus	WM	–
MDD > SCZ	Cluster 1	283	−50	8	−20	Left	Temporal	Superior Temporal Gyrus	GM	38
						Left	Temporal	Superior Temporal Gyrus	GM	22
						Left	Temporal	Superior Temporal Gyrus	WM	–
	Cluster 2	81	−34	18	−30	Left	Temporal	Superior Temporal Gyrus	GM	38
						Left	Frontal	Inferior Frontal Gyrus	WM	–
Investigator 2										
						Main area in the cluster				
Direction of effect	Cluster	Number of voxels	X	Y	Z	Hemisphere	Lobe	Cortical area	GM/WM	Brodmann area
HC > MDD	Cluster 1	16,602	1	−2	26	Right	Frontal	Superior Frontal Gyrus	WM	–
						Right	Frontal	Middle Frontal Gyrus	WM	–
						Left	Frontal	Superior Frontal Gyrus	WM	–
						Left	Frontal	Middle Frontal Gyrus	WM	–
	Cluster 2	46	−36	−8	16	Left	Sub lobar	Insula	GM	13
						Left	Sub lobar	Insula	WM	–
	Cluster 3	43	–32	22	8	Left	Frontal	Sub Gyral	WM	–
						Left	Sub lobar	Insula	GM	13
						Left	Sub lobar	Extra Nuclear	WM	–
HC > SCZ	Cluster 1	4728	−4	26	58	Right	Frontal	Superior Frontal Gyrus	WM	–
						Right	Frontal	Middle Frontal Gyrus	WM	–
						Right	Frontal	Precentral Gyrus	WM	–
						Right	Frontal	Sub Gyral	WM	–
						Left	Frontal	Superior Frontal Gyrus	WM	–
	Cluster 2	80	32	−28	60	Right	Frontal	Precentral Gyrus	GM	4
						Right	Frontal	Precentral Gyrus	WM	–
						Right	Parietal	Postcentral Gyrus	GM	3
	Cluster 3	51	36	−10	8	Right	Sub lobar	Insula	WM	–
						Right	Sub lobar	Extra Nuclear	WM	–

Abbreviations: SCZ = Schizophrenia, MDD = Major depressive disorder, HC = Healthy control, GM = Grey matter, WM = White matter.

a significant trend ($p < 0.1$) for HC and MDD patients (Table S2). The correlation between the difference in Euclidean distance of XYZ electrode placement of investigator 2 minus investigator 1 and the difference between the number of significantly activated e-field voxels between investigator 2 minus investigator 1 showed a significant negative correlation for MDD with F3 (Pearson's $r = -0.587$, $p = 0.002$, 95% CI = −0.797, −0.25) and F4 electrode (Pearson's $r = -0.607$, $p = 0.002$, 95% CI = −0.808, −0.278) as well as SCZ with F3 (Pearson's $r = -0.433$, $p = 0.031$, 95% CI = −0.71, −0.05) and F4 (Pearson's $r = -0.373$, $p = 0.066$, 95% CI = −0.67–0.03). For the HC, a negative significant trend was observed at F3 (Pearson's $r = -0.406$, $p = 0.067$, 95% CI = −0.71–0.03) and F4 (Pearson's $r = -0.386$, $p = 0.084$, 95% CI = −0.70, 0.06) (Fig. S1).

3.5. Inter-individual difference

The standard deviation (SD) of the e-field value increased with raising the percentile threshold of the voxels. It indicates the inter-individual difference of the e-field intensity at higher-cap; the maximum e-field strength considerably varies inter-individually (Fig. 5A). Additionally, Fig. 5B shows three selected surface-based individual e-field models from each group, illustrating that there are individuals with relatively higher or lower e-fields. Even though there were significant cross-diagnostic differences, inter-individual differences within each group were noticeable.

4. Discussion

In a cross-diagnostic comparison of MDD and SCZ patients with HC, this study investigates the strength and distribution of individually modeled e-fields for bifrontal tDCS as applied in numerous clinical studies investigating therapeutic tDCS. To the best of our knowledge, this is the first study comparing tDCS-induced e-fields in patients with major psychiatric disorders and HC to test a basic assumption in the field, namely the translation of stimulation parameters from healthy subjects to clinical samples. Our main finding was that the average e-field strength considerably varied across subjects and was significantly lower in MDD and SCZ patients compared to HC. However, there was no significant difference in e-field intensity between both clinical samples. The difference between SCZ and HC was consistently found by both investigators for bilateral superior frontal gyrus and right middle frontal gyrus regions. Focusing on PFC ROIs, significant differences in e-field intensity between MDD and HC as well as SCZ and HC were consistently observed by both investigators for Sallet 8B and 9 regions, though the difference between MDD and SCZ did not reach statistical significance in any Sallet regions. In addition, there were marked differences in e-field intensities between investigators, though the number of two investigators does not allow to establish a valid estimate of inter-rater variability. On a descriptive level, we observed considerable inter-individual variability of e-field intensity within groups.

4.1. E-field intensity difference between clinical populations and healthy subjects

The present study showed that e-field intensity was lower in MDD and SCZ compared to HC with both whole-brain and PFC ROI-based analysis. E-field modeling was based on morphometric information from individual structural MRI scans. The changes in GM volumes and

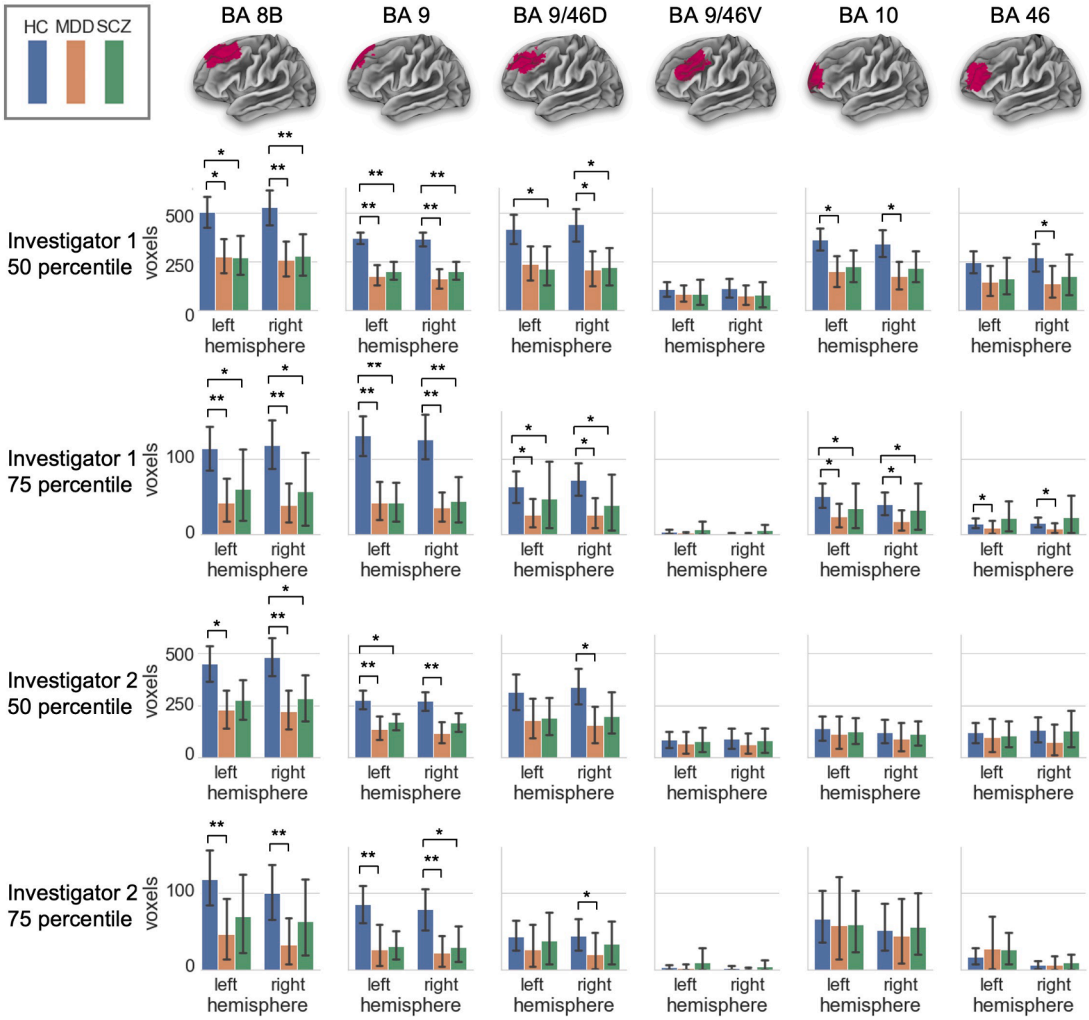

Fig. 4. Group variability of e-field strength in PFC parcellated by Sallet atlas. The maximum e-field values in PFC were averaged among all subjects, and its 50th and 75th percentile values were used as the threshold. The graph shows the number of voxels which exceeded the threshold in each PFC area from both investigators 1 and 2. * = $p < 0.007$, ** = $p < 0.0001$.

cortical thickness in clinical samples may contribute to the differences between clinical and non-clinical samples. There is comprehensive evidence of both GM atrophy in MDD (Chang et al., 2011; Du et al., 2014; Shah et al., 1998; Wise et al., 2017) and SCZ (Fornito et al., 2009; Théberge et al., 2007; Whitford et al., 2006) as well as reduced cortical thickness in MDD (Mackin et al., 2013; Rajkowska et al., 1999) and SCZ (Goldman et al., 2009; Narr et al., 2005; Rimol et al., 2010; Schultz et al., 2010; van Haren et al., 2011). However, the e-field differences between clinical populations and healthy controls are related to the structural MRI data and it does not inform about the overall translational validity from health to disease. A multitude of factors (e.g. neurochemical and molecular changes, functional network alterations, behavioral and cognitive differences) may impact the capacity for the translation even if e-field strengths are adjusted for clinical groups or individual patients.

In the light of our previous study that showed an association between the GM volume in the dorsal PFC and treatment outcome in the MDD (Bulubas et al., 2019), e-field modeling may play a future role in predicting NIBS outcome (Albizu et al., 2020; Suen et al., 2021). In SCZ, Mondino et al. (2021) recently reported that tDCS responders showed a higher e-field strength in the left transverse temporal gyrus at baseline compared to non-responders. Nevertheless, the interaction of e-fields with the individual anatomy is complex (Antonenko et al., 2021a). Though e-fields may represent a valid proxy for individually adjusted tDCS intensity, one has to keep in mind that dose–response relationships have not yet been established for tDCS and intensity is only one parameter of tDCS "dosage" which may not follow simplistic models.

4.2. *Importance of precise electrode positioning*

The current study used a python script that allowed two blinded investigators to calculate F3 and F4 positions based on nasion, inion, and mastoids coordinates. This approach imitated current clinical practice where operators use the international 10–20 EEG system for positioning tDCS electrodes over F3 and F4. Hence, it enabled us to investigate whether tDCS-induced e-fields differ between two investigators who determined the electrodes' position and orientation independently. Though there was a high intraclass correlation between both investigators, there were also discrepancies in electrode positions and related e-field intensities. The spatial distribution of e-fields showed that investigator 1 tended to place the electrodes slightly differently than investigator 2, which is due to individual variation in implementation although the instruction was the same. Even such a small variation in positioning led to different statistical results derived from the discrepancies in the e-field distribution. In practice, this finding adds to the previous report by Opitz et al. (2018) who suggested limiting the electrode positioning error to be plus/minus 1 cm for achieving consistent results. The importance of precise electrode positioning must be emphasized here again because it can be easily forgotten as tES is a

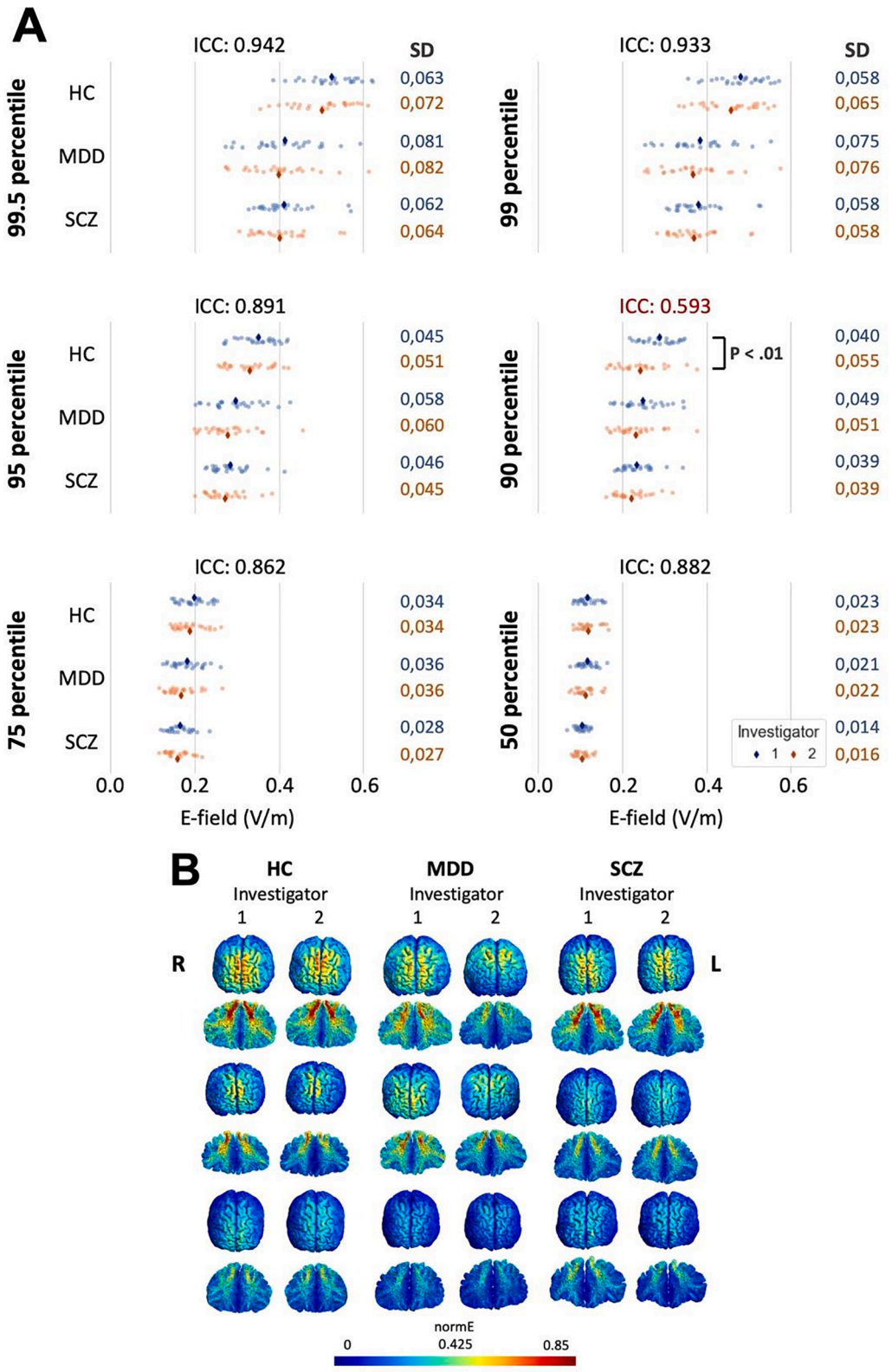

Fig. 5. A) distribution of e-field value classified by subject groups, investigators, and percentile thresholds of the voxels. Every dot indicates an individual's e-field value which falls at each percentile when all voxels are listed in the order of e-field strength. Graph with higher percentile shows higher standard deviation (SD) which indicates inter-individual differences of simulated e-field values. Intraclass correlation (ICC) was high except for 90th percentile values. B) Spatial e-field distribution from selected 3 subjects in each subject group simulated by 2 investigators. E-field strength is reflected in each subject's individual space (whole-brain and sagittal view cut at the temporal pole). It shows that the e-field value of patients can be as high as HC, and HC may also have as low e-field as patients. Though the group difference is significant, the inter-individual difference is prominent.

rather non-focal NIBS approach. Neuronavigation algorithms may represent valid approaches for precise electrode montages in tES applications (Jog et al. 2021).

4.3. Inter-individual variability of e-field

Another observation replicated from other studies (Seibt et al., 2015) is the considerable inter-individual differences in field strength and distribution which may be hidden under the group average. Even though there was a significant difference in group averages between clinical samples and HCs, it is noteworthy that there were patients who showed high-intensity e-fields comparable with HC, and there were HC subjects who showed low e-field strength at the level of other MDD and SCZ patients. Inter-individual differences in e-fields may be attributed to the variability of the treatment response, as e-fields intensity reflects the effect of the stimulation. Antonenko et al. (2021b) identified that head, skull, skin, and CSF volumes as anatomical variables explaining a major proportion of variability in general field strength and proposed to consider these parameters for empirical tDCS studies. As every brain has individual attributes which yield variability in e-fields, it is suggested to refer to the e-field information when deciding the stimulation parameters.

4.4. Individualization of tDCS

In conclusion, the question arises whether the fixed dosing (usually defined by x mA) for tES application should be replaced by individualized dosing regimes based on individual e-field modeling. Previous studies have shown that e-field intensity differs by more than 100% across subjects when electrodes are located at the conventional stimulation site of the primary motor cortex (Evans et al., 2020), and the inter-individual variability even increases further with focal montages (Mikkonen et al., 2020). Furthermore, the inter-individual difference in the e-field was associated with variability in the tES outcome (Kasten et al., 2019). When only group differences are considered, the inter-individual difference is masked by the group effect. For the future of tES, controlling for inter-individual and inter-rater variability will become a key to establishing more stable therapeutic effects.

4.5. Current limitation and future perspectives

The present study demonstrated the importance of the individualization of the tDCS protocol. Recent studies show that network-based approaches, such as e-field modeling or FC and connectome analyses with fMRI, contribute to the stratification or individualization of NIBS (Chen et al., 2018; Soleimani et al., 2021). E-field modeling is a relatively quick and simple but informative and meaningful method to define the stimulation dosage, electrode location, and montage depending on the individual brain structure. Additionally, since our two investigators showed different results, we suggest paying attention to the electrode localization variability occurring unconsciously, for example by using neuro-navigation.

Even though the stimulation strength and electrode locations are controlled, there are still other factors that are assumed to cause differences in the patient's responsiveness. For example, brain state is a factor known to affect the ability to respond to tES but is difficult to control. Individual levels of fatigue, arousal, attention, anxiety, and excitement at the moment of the brain stimulation are potentially the confounding factors that modulate the outcome of the tDCS treatment (Krause and Cohen Kadosh, 2014). Additionally, circadian rhythm and hormonal levels could be also a source of variability (Krause and Cohen Kadosh, 2014). Since we have these almost uncontrollable sources of individual variability, we suggest at least controlling for e-field intensity for each individual.

The interpretation of our results should take into account the limitations that arise from the computational e-field modeling. First, the calculated e-field in this study is based on the individual anatomical features, meaning that it is only a proxy for the real e-field and stimulation. A kind of e-field validation can be obtained through in-vivo invasive electrophysiological recordings (Opitz et al., 2018; Wang et al., 2022). Second, in the present study, e-field modeling was based on the T1-weighted anatomical scans. However, it is recommended for future studies to also include T2-weighted images to improve the accuracy of CSF-skull segmentation. Lastly, to improve the quality of the e-field modeling, further research is needed to investigate the conductivity variance between individuals. With the current system, the conductivity is set at the same default value for all individuals. However, some previous studies showed that the calcification change related to aging causes a significant conductivity change in the skull for example (Hoekema et al., 2003; McCann et al., 2019).

Finally, our study has focused on one montage only, i.e. the standard F3-F4 montage used for therapeutic intervention in MDD (Bajbouj et al., 2018; Blumberger et al., 2012; Brunoni et al., 2013; Padberg et al., 2017). In the milestone ELECT-TDCS trial by Brunoni et al. (2017), a very similar montage has been applied to MDD, i.e. anode over left DLPFC and cathode over right DLPFC according to the Omni-Lateral Electrode (OLE) system (Seibt et al., 2015). In SCZ research, several studies have applied the F3 target for positioning the anode, however, the cathode position has been varied across studies (Palm et al., 2016; Valiengo et al., 2020). Recently, Antonenko et al. (2021a) applied SimNIBS modeling to six tDCS montages and introduced a measure of e-field focality determined by the area of the GM region with the field strengths higher than the 75th percentile, where higher values represent higher current spread, implying lower focality. In the second study, Antonenko et al. (2021b) compared four bipolar montages and four "focal" 4x1 montages and proposed the individual head circumference as a proxy for estimating individual differences in the tDCS induced e-field. Future studies should also investigate e-field parameters for different montages in comparison between clinical and non-clinical groups.

5. Conclusion

Our results revealed two important findings: 1) the mean strength of tDCS-induced e-fields based on the standard anode-F3/cathode-F4 bipolar montage is lower in MDD and SCZ compared to HC, but MDD and SCZ groups does not differ significantly either at the whole-brain level or on PFC ROI analysis. 2) Inter-individual and inter-rater differences are prominent and should not be ignored. The present study supports the hypothesis that dose–response relationships cannot be simply transferred from healthy cohorts and need to be specifically established for clinical groups, possibly using the MRI-based e-field strength as a proxy for individual dosing.

Further research is needed to develop predictors for therapeutic effects based on e-field models and to establish dose–response relationships for clinical applications.

6. Open Science Framework (OSF)

To support the Open Science approach and for transparency reasons, we have published our data at OSF: https://osf.io/74tz9/?view_only=eca19c741793403fa88379f4d30b979a.

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CRediT authorship contribution statement

Yuki Mizutani-Tiebel: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **Shun Takahashi:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing. **Temmuz Karali:** Software. **Eva Mezger:** Conceptualization, Methodology. **Lucia Bulubas:** Conceptualization, Methodology. **Irina Papazova:** Investigation. **Esther Dechantsreiter:** Conceptualization, Methodology. **Sophia Stoecklein:** Investigation. **Boris Papazov:** Investigation. **Axel Thielscher:** Methodology, Supervision. **Frank Padberg:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. **Daniel Keeser:** Conceptualization, Methodology, Formal analysis, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The work of YM is part of a Ph.D. thesis of Munich medical research school, university hospital LMU. YM receives remuneration from neuroCare Group AG as a part-time office worker. AT is supported by the Innovation Fund Denmark (IFD) - grant agreement number 9068-00025B and was supported by the Lundbeck foundation (R244-2017-196 and R313-2019-622). FP is a member of the European Scientific Advisory Board of Brainsway Inc., Jerusalem, Israel, and the International Scientific Advisory Board of Sooma, Helsinki, Finland. He has received speaker's honoraria from Mag&More GmbH, the neuroCare Group, Munich, Germany, and Brainsway Inc. His lab has received support with equipment from neuroConn GmbH, Ilmenau, Germany, Mag&More GmbH and Brainsway Inc. Other authors reported no biomedical financial interests or potential conflicts of interest.

Appendix A. Supplementary data

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6. Paper II

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Computational modeling of electric fields for prefrontal tDCS across patients with schizophrenia and mood disorders

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ABSTRACT

This cross-diagnostic study aims to computationally model electric field (efield) for prefrontal transcranial direct current stimulation in mood disorders and schizophrenia. Enrolled were patients with major depressive disorder (n = 23), bipolar disorder (n = 24), schizophrenia (n = 23), and healthy controls (n = 23). The efield was simulated using SimNIBS software (ver.2.1.1). Electrodes were placed at the left and right prefrontal areas and the current intensity was set to 2 mA intensity. Schizophrenia and major depressive disorder groups showed significantly lower 99.5th percentile efield strength than healthy controls. In voxel-wise analysis, patients with schizophrenia showed a significant reduction of simulated efield strength in the bilateral frontal lobe, cerebellum and brain stem compared with healthy controls. Among the patients with schizophrenia, reduction of simulated efield strength was not significantly correlated with psychiatric symptoms or global functioning. The patients with bipolar disorder showed no significant difference in simulated efield strength compared with healthy controls, and there was no significant difference between the clinical groups. Our results suggest attenuated electrophysiological response to transcranial direct current stimulation to the prefrontal cortex in patients with schizophrenia, and to some extent in patients with major depressive disorder.

1. Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive stimulation technique that modulates cortical excitability by applying a minute direct current from outside the skull. Efficacy of tDCS has been reported for major psychiatric disorders, such as major depressive disorder (MDD) (Brunoni et al., 2017; Sharafi et al., 2019; Mutz et al., 2018; Razza et al., 2021; Zhang et al., 2021), bipolar disorder (BP) (Loo et al., 2018; Mutz et al., 2018; Dondé et al., 2018; Yamada et al., 2020), and schizophrenia (SCZ) (Brunelin et al., 2012; Smith et al., 2015; Palm et al., 2016; Chang et al., 2019; Cheng et al., 2020; Yamada et al., 2020; Tseng et al., 2022). On the other hand, some clinical studies on prefrontal tDCS for treatment-resistant depression (Blumberger et al., 2012; Berlim et al., 2013) and for SCZ (Fitzgerald et al., 2014) failed to show significant treatment effectiveness. Optimal indications and stimulation parameters continue to be investigated.

The electric field (efield), defined as the electric force per unit charge, is produced in the brain when direct current is applied by

Abbreviations: tDCS, transcranial direct current stimulation; MDD, major depressive disorder; BP, bipolar disorder; SCZ, schizophrenia; HC, healthy control; MRI, magnetic resonance image; efield, electric field; DLPFC, dorsolateral prefrontal cortex; HAMD, Hamilton Depression Rating Scale; PANSS, Positive and Negative Symptoms Scores; YMRS, Young Mania Rating Scale; GAF, Global Assessment of Functioning; FSL, FMRIB software Library; HSD, honestly significant difference; ICC, intraclass correlation coefficient.

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electrodes to the scalp. In the early 2010s, efield during tDCS was begun to be simulated using realistic MRI-derived head model (Parazzini et al., 2011). SimNIBS is a software package for simulating the efield generated by tDCS (Thielscher et al., 2015). The major tissues of the head (white matter and gray matter, cerebrospinal fluid, the skull, the scalp and the eyeballs) are identified from the structural images taken by magnetic resonance image (MRI), and the efield generated by tDCS is simulated by setting the conductivity in each tissue (Windhoff et al., 2013; Saturnino et al., 2019; Padberg et al., 2021). Csifcsák et al. (2018) conducted efield simulation using SimNIBS in 19 patients with MDD and 19 healthy controls (HC). The simulated efield was similar in both groups. Elsewhere, Suen et al. (2021) reported that a higher simulated efield strength at the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulate cortex corresponds to a more pronounced decrease of depressive symptoms as measured by the Positive and Negative Affect Scale and Hamilton Depression Rating Scale (HAMD). More recently, Mizutani-Tiebel et al. (2022) reported reduced simulated efields in MDD and SCZ groups than in HC group. The simulated efields in tDCS in patients with BP or SCZ have not been widely investigated, and to our knowledge, no studies have compared simulated efield across patients with MDD, BP and SCZ.

There is great variation in efield generated by tDCS (Krause et al., 2014; Wiethoff et al., 2014; Horvath et al., 2014; Mizutani-Tiebel et al., 2022) owing to individual structural and functional neuroanatomical differences (Opitz et al., 2016; Huang et al., 2017; Antonenko et al., 2021; Mosayebi-Samani et al., 2021). Recently, Mezger et al. (2020) reported low clinical efficacy of tDCS with low simulated efield in a patient with schizophrenia with left frontal lesion. Structural abnormalities in the gray and white matter have been detected in individuals with mood disorders (Lim et al., 1999; McKinnon et al., 2009; Beyer et al., 2009; Bora et al., 2012; Lai, 2013; Yamada et al., 2015, 2020) and in individuals with SCZ (Lim et al., 1999; Steen et al., 2006; Ohoshi et al., 2019; Yamada et al., 2020). Their relations with severity and neuropsychological scale have also been reported (Moore et al., 2001; Cahn et al., 2006; Bora et al., 2012; Yamada et al., 2015; Ohoshi et al., 2019; Yamada et al., 2020). In addition to individual differences in skin and skull thickness, pathological structural changes in the brain may affect the efield generated by tDCS and contribute to individual differences in the effects of tDCS. This study aims to compare the simulated efield strength of tDCS between patients with SCZ, MDD, BP, and HC, and to examine the relation of the simulated efield with global function and psychiatric symptoms.

2. Methods

2.1. Participants

Participants comprised 23 patients with MDD, 24 with BP, 23 with SCZ, and 23 with HC (Table 1). Imaging and clinical data were gathered from our previous research projects, but Wakayama Medical University Hospital Ethics Committee approved secondary use of the cohort in this present study (No. 2633). The study was conducted in accordance with the tenets of the Declaration of Helsinki. Patients were all recruited from the Wakayama Medical University Hospital. Two well-experienced and independent psychiatrists who are certified by the Japanese Society of Psychiatry and Neurology diagnosed patients based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. One psychiatrist examined the patients face-to-face and the other examined the validity of the diagnosis by checking medical records. Patients with comorbid psychiatric or medical illness, or substance or alcohol abuse were excluded. Subjects with structural abnormalities on MRI except for asymptomatic arachnoid cysts were also excluded. Psychiatric symptoms were assessed using Positive and Negative Symptoms Scores (PANSS) for SCZ group, HAMD was used for MDD and BP groups, Young Mania Rating Scale (YMRS) was used for the BP group, and Global Assessment of Functioning (GAF) scale was used in all patients. In the SCZ group, antipsychotic medication was calculated as chlorpromazine-equivalent doses (Inada and Inagaki, 2015).

2.2. MRI data acquisition and processing

We acquired anatomical MRI data on a 3.0T MR scanner (Achieva TX 3.0T; Philips Medical Systems) using a 32-element sensitivity-encoding head coil. A 3D fast field echo T1-weighted sequence was used for anatomical MRI (TR/TE = 7.0/3.3 ms, FOV = 220 mm, 210 slices, acquisition voxel size = 0.86 × 0.86 × 0.90 mm, and a slice thickness = 0.9 mm). To simulate the efield, we used SimNIBS version 2.1.1 (Thielscher et al., 2015) under FreeSurfer software version 6.0 (https://surfer.nmr.mgh.harvard.edu/) and FMRIB software Library (FSL) version 5.0.5 (Smith et al., 2004). A command line script "mri2mesh" on SimNIBS was used to automatically create a tetrahedral mesh of the volume of the head. Segmentation of brain structures was checked visually by S.U. (Investigator 1) and A.T. (Investigator 2).

2.3. Simulation

The two investigators independently conducted SimNIBS simulation on the same cohort after being blinded to subjects' diagnosis, clinical symptoms, age, and sex. The tDCS electrodes were placed with anode and cathode electrodes at F3 and at F4, respectively, according to the international 10–20 system. These stimulation sites were recommended in the evidence-based guidelines for tDCS treatment of patients with MDD (Fregni et al., 2021) and some previous tDCS clinical studies used same montage setting for patients with BP (Sampaio-Junior et al., 2018) or SCZ (Shiozawa et al., 2016). The subjects' diagnoses were blinded in this study, so we used the bifrontal montage setting that is commonly

Table 1
Demographic and clinical data of the subjects.

	HC group (n = 23)		SCZ group (n = 23)		BP group (n = 24)		MDD group (n = 23)		P value
Male/Female	13/10		12/11		16/8		16/7		0.576 [a]
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
age (range 20 to 65 years old)	40.91	10.04	45.3	10.17	39.29	11.73	43.57	8.82	0.187 [b]
duration of illness (years)			20.09	12.17	8.78 [c]	10.05 [c]	3.8	6.57	
PANSS positive score			13.65	5.42					
PANSS negative score			17.43	6.17					
PANSS general psychopathology score			31.39	1.08					
PANSS total score			62.48	20.71					
HAMD-17 score					4.93	5.65	8.96	6.02	
YMRS score					2.25	3.3			
GAF score			59.78	14.02	73.17	14.91	64.28 [d]	17.70 [d]	
antipsychotic medication dose (chlorpromazine equivalent)			562.09	332.93					

HC: healthy controls, SCZ: patients with schizophrenia, BP: patients with bipolar disorder, MDD: patients with major depressive disorder, SD: standard deviation, PANSS: Positive and Negative Syndrome Scale, HAMD: Hamilton Depression Rating Scale, YMRS: Young Mania Rating Scale, GAF: Global Assessment Functioning. a: chi-squared test, b: Kruskal-Wallis test, c: n = 23, d: n = 18.

used for patients with MDD (Brunoni et al., 2017) for all groups. The locations of F3 and F4 were automatically determined by SimNIBS program and direction of electrodes was manually adjusted. We set the size of the electrodes to a rectangular size of 4.5 cm x 6.5 cm, the electrode thickness to 5 mm, and the saline-soaked sponge thickness to 6 mm. Current intensities were set at 2 mA on the F3 and −2 mA on the F4. Conductivity was set at the default SimNIBS settings (white matter: 0.126 S/m, gray matter: 0.275 S/m, cerebrospinal fluid: 1.654 S/m, the skull: 0.010 S/m the skin: 0.465 S/m, and the eyeballs 0.500 S/m). The simulated efield was automatically projected to MNI standard space by SimNIBS software in each subject. The efield strength is represented as "norm E" in SimNIBS software. The norm corresponds to the vector size of the efield, it therefore always takes positive value without information about the efield direction (Saturnino et al., 2019). The efield strength was then calculated at 75th, 90th, 95th, 99th, 99.5th percentiles with SimNIBS.

2.4. Statistics

IBM SPSS Statistics software (version 22.0, IBM Japan Tokyo, Japan) was used for statistical calculation. The Shapiro-Wilk test revealed that the age of HC group was not distributed normally ($P = 0.043$), so Kruskal-Wallis H test was used to assess the differences of age between the groups. Difference of gender distribution between groups was examined by chi-squared test.

Shapiro-Wilk test was used for assessment of normality of simulated efield strength in each percentile. In order to examine differences of simulated efield strength in each percentile among the groups, analysis of variance and the post-hoc Tukey's honestly significant difference (HSD) test were used in the normally distributed percentile simulated efield strength. Kruskal-Wallis H test and the post hoc Mann–Whitney U test were used in the non-normally distributed percentiles simulated efield strength. Inter-rater reliability was tested using the intraclass correlation coefficient (ICC) test in the normally distributed percentile simulated efield strength.

In voxel-wise analysis, group differences of simulated efield strength were assessed using randomize program (Ver.2.9) (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/randomize/UserGuide) on FSL with age and sex as covariates. Statistical significance was set to $P < 0.008$ (Bonferroni correction; $P = 0.05/6$ tests: HC vs MDD, HC vs BP, HC vs SCZ, MDD vs BP, MDD vs SCZ, BP vs SCZ). In order to explore the relationship between the efield strength and clinical characteristics, duration of illness or dose of antipsychotic medication voxel-wise multiple regression analysis was conducted using randomize program (ver.2.9) with age and sex as covariates in the voxels that showed significant difference of efield strength between the groups. Statistical significance was set to $P < 0.05$ / number of tests (Bonferroni correction).

3. Results

The difference of age and gender balance between the groups was not statistically significant (Table 1). Shapiro-Wilk test showed that Investigator 1 had normal distributions of simulated efield strength in 99.5th percentile and Investigator 2 had normal distributions of simulated efield strength in 99.5th, 90th and 75th percentiles, while the others did not. Analysis of variance and the post hoc Tukey's HSD test showed that the simulated efield strength of the HC group was significantly higher in 99.5th percentile compared with the SCZ and MDD groups according to Investigator 1 (Fig. 1, Table 2) and Investigator 2 (Supplementary Fig. 1, Table 2). ICC of 99.5th percentile simulated efield strength between Investigator 1 and 2 was 0.988. In voxel-wise analysis, simulated efield strength was reduced in the bilateral frontal area, brain stem and cerebellum in the SCZ group compared with the HC group in analysis according to both Investigators 1 and 2 (Fig. 2). Individual simulated efield of all subjects is shown in Supplementary Fig. 2, while individual simulated efield at the horizontal fissure of cerebellum of the HC and SCZ groups are shown in Supplementary Fig. 3. The MDD or BP groups were not shown to have significant differences of simulated efield compared with the HC group, simulated efields were not significantly different between the patient groups. In the SCZ group, there were no significant relations between reduced simulated efield and clinical characteristics (i.e. PANSS positive, negative, general

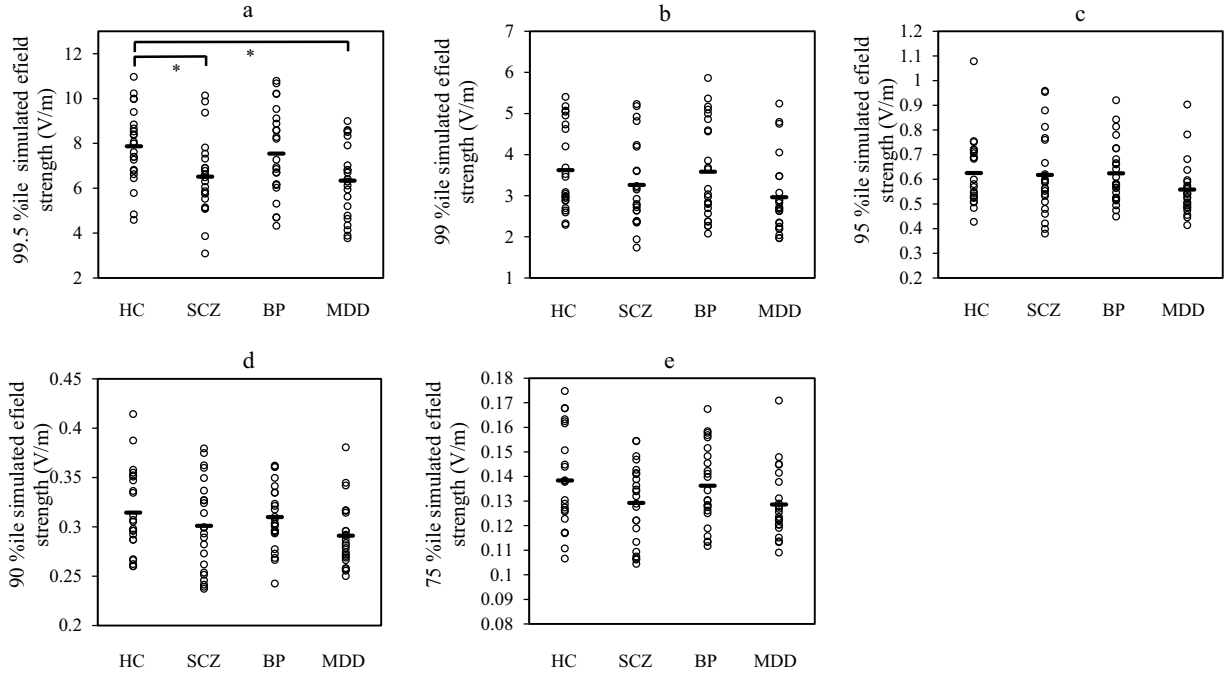

Fig. 1. Scattergram of simulated efield strength in each percentile value in four groups in Investigator 1. The circles show individual simulated efield strength and the short bar indicates the mean value of each group. The HC group shows higher simulated efield strength than the SCZ and MDD groups in 99.5th percentile (* $P < 0.05$). HC: healthy control, SCZ: schizophrenia, BP: bipolar disorder, MDD: major depressive disorder.

Table 2
Differences of simulated efield strengths among the groups in each percentile.

	HC group ($n = 23$)		SCZ group ($n = 23$)		BP group ($n = 24$)		MDD group ($n = 23$)		Statistics	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Investigator 1										
99.5%ile value [a]	7.87	1.65	6.52	1.70	7.55	1.95	6.34	1.62	$F = 4.343$	$P = 0.007$* HC > SCZ, MDD > SCZ
									post hoc	HC > SCZ ($P = 0.048$*), MDD > SCZ ($P = 0.019$*)
99%ile value [b]	3.62	1.03	3.26	1.04	3.58	1.18	2.96	0.93	$\chi2 = 7.162$	$P = 0.067$
95%ile value [b]	0.63	0.14	0.62	0.17	0.62	0.12	0.56	0.11	$\chi2 = 5.301$	$P = 0.151$
90%ile value [b]	0.31	0.04	0.30	0.05	0.31	0.03	0.29	0.03	$\chi2 = 5.687$	$P = 0.128$
75%ile value [b]	0.14	0.02	0.13	0.02	0.14	0.02	0.13	0.01	$\chi2 = 4.660$	$P = 0.198$
Investigator 2										
99.5%ile value [a]	7.85	1.61	6.54	1.70	7.46	1.83	6.30	1.63	$F = 4.304$	$P = 0.007$* HC > SCZ, MDD > SCZ
									post hoc	HC > SCZ ($P = 0.04951$*), MDD > SCZ ($P = 0.014$*)
99%ile value [b]	3.60	1.00	3.27	1.03	3.58	1.17	2.95	0.93	$\chi2 = 7.140$	$P = 0.068$
95%ile value [b]	0.64	0.13	0.63	0.17	0.64	0.13	0.57	0.11	$\chi2 = 5.453$	$P = 0.141$
90%ile value [a]	0.32	0.04	0.31	0.05	0.32	0.03	0.30	0.03	$F = 1.924$	$P = 0.131$
75%ile value [a]	0.14	0.02	0.13	0.02	0.14	0.02	0.13	0.01	$F = 2.531$	$P = 0.062$

Significant differences among the 4 groups are marked *. ($P < 0.05$).
a: Analysis of variance and the post hoc Tukey's honestly significant difference test.
b: Kruskal-Wallis test.
HC: healthy controls, SCZ: schizophrenia, BP: bipolar disorder, MDD: major depressive disorder, SD: standard deviation.

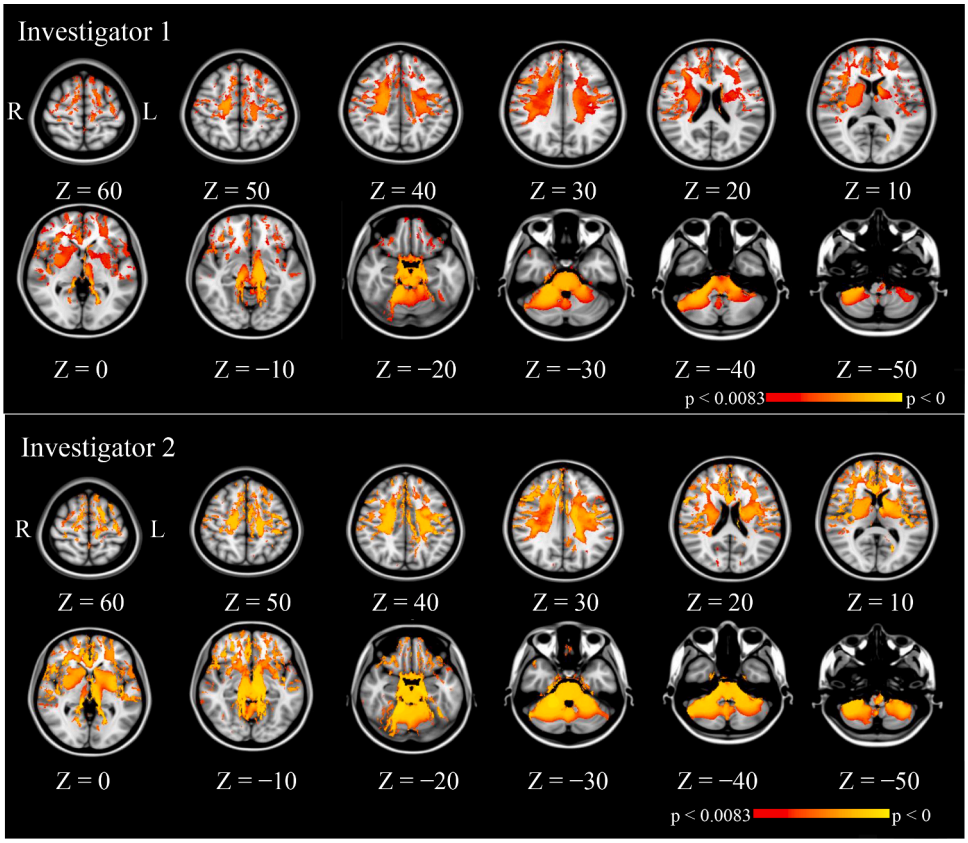

Fig. 2. Difference of simulated efield strength between the SCZ and HC groups in voxel-wise analysis. Yellow-Red voxels indicate regions where the simulated efield strength of the SCZ group is significantly lower than that in the HC group.

psychopathological scores and GAF score), duration of illness, or dose of antipsychotic medication according to analysis by the two investigators.

4. Discussion

To our knowledge, this is the first study to compare the simulated efield strength by tDCS across such a wider spectrum of clinical conditions, including SCZ, MDD and BP. In the 99.5th percentile, significantly higher simulated efield strength was shown in the HC group than in the SCZ and MDD groups in analysis by both of the investigators. In voxel-wise analysis by both investigators, the simulated efield strength was significantly reduced in the bilateral frontal region, brainstem, and cerebellum in the SCZ group compared with the HC group. In the SCZ group, the reduction of the simulated efield strength was not related to global function or psychiatric symptoms. The MDD or BP groups showed no significant differences of simulated efield strength compared with the HC group, and there was no significant difference of simulated efield strength between the disorder groups.

The simulated efield was significantly reduced in the SCZ group compared with the HC group in percentile values and voxel-wise

analysis, suggesting that the electrophysiological response to tDCS to bifrontal cortex is attenuated in patients with SCZ. Regarding tDCS for patients with SCZ, previous meta-analyses have shown efficacy on auditory hallucination and negative symptoms (Cheng et al., 2020), but some studies have reported no significant effect of tDCS on psychiatric symptoms (Fitzgerald et al., 2014; Fröhlich et al., 2016). Based on our finding of reduced simulated efield in the SCZ group, the stimulation intensity may need to be increased in tDCS treatment for patients with SCZ. Supporting this hypothesis, a recent case report showed a patient with tDCS-resistant schizophrenia with reduction of simulated efield for left prefrontal tissue lesion (Mezger et al., 2020). The individual variability of therapeutic effect or simulated efields of tDCS has been shown in several clinical studies (Bennabi and Haffen, 2018; Mizutani-Tiebel et al., 2022). In line with these individual differences in previous clinical studies, our results of simulated efield widely varied between all subjects, including patients with SCZ. To improve treatment efficacy of tDCS in patients with SCZ, further investigation of appropriate stimulation parameters regarding individual electrical conductivity is needed.

Interestingly, in the SCZ group, reduced simulated efield strength was shown in the brain stem and cerebellum as well as in the frontal region. Volume reduction in the hippocampus, left thalamus, right nucleus accumbens, left cerebellar cortex, and brain stem in patients with SCZ and BP was highlighted in a previous study (Rimol et al., 2010). In addition, a diffusion tensor imaging study reported a reduction of fractional anisotropy values at the site which included the brain stem in antipsychotic drug-naive patients with SCZ (Alvarado-Alanis et al., 2015). A relation between dysfunction of the cerebellar-prefrontal cortex and negative symptoms was identified using functional MRI and repetitive transcranial magnetic stimulation (Brady et al., 2019). A review of the clinical effects of cerebellar stimulation using tDCS or transcranial magnetic stimulation in patients with SCZ mainly showed improvement in negative symptoms, cognitive function, and depression (Escelsior et al., 2019). The reduction of simulated efield strength of the brainstem and the cerebellum in our SCZ group may reflect insufficient remote effect to the brainstem or cerebellum during tDCS to the frontal cortex in patients with SCZ.

In this study, reduced simulated efield strength was not significantly associated with global function, duration of illness, dose of antipsychotic medication or clinical symptoms in the SCZ group. Simulated efield was generalized from structural imaging data in SimNIBS analysis, so the reduced simulated efield strength in the SCZ group suggests that structural pathology impacts upon electrophysiological response during prefrontal tDCS in patients with SCZ. No significant association between reduced simulated efield strength and global function and clinical symptoms was shown in our results, but further research is needed to elucidate the relationship between changes of simulated efield and clinical characteristics in patients with SCZ.

The MDD group showed reduced efield strength in 99.5th percentile compared with the HC group, while the other percentiles and voxel-wise analysis showed no significant differences between the MDD and HC groups. These results suggest that differences of simulated efield strength between the MDD and HC groups were not robust and that the 99.5th percentile efield strength is sensitive for revealing differences between groups. Using SimNIBS, Csifcsák et al. (2018) reported significantly reduced simulated efield strength in patients with MDD compared with HC in a tiny area along the superior frontal sulcus during bifrontal tDCS. Mizutani-Tiebel et al. (2022) showed the reduction of simulated efield in MDD group. Differences of simulated efield were not large in either our study or the previous studies (Csifcsák et al., 2018; Mizutani-Tiebel et al., 2022), so further research with characteristics-controlled large size cohort is needed to reveal changes of simulated efield during tDCS in patients with MDD.

Large inter-individual variability was shown in our study within the groups (Supplementary Figs. 2 and 3), and inter-individual variability outweighed the variability between the groups (Fig. 1 and Supplementary Fig. 1). Inter-individual fluctuations in efield strength caused by tDCS have been repeatedly highlighted in previous simulation studies, and Laakso et al. (2015) reported that half of inter-individual variation is regulated by the volume of cerebrospinal fluid. Bulubas et al. (2019) reported a positive correlation between the antidepressant effect of tDCS and the gray matter volume of the left prefrontal cortex, suggesting that anatomical features may influence the effect of tDCS. Evans et al. (2020) showed that fixed-dose tDCS varies efield intensity in the brain across individuals and that dose-controlling may reduce variance. These findings and our results of inter-individual variability of simulated efield strength suggest the importance of individually adjusting the stimulus settings.

In this present study, the position of tDCS electrodes was arranged according to the EEG international 10–20 system. The positions of electrodes were finely adjusted manually, so there were slight differences in the location and angle of the electrodes for each investigator. Electrode positioning is considered one of the most important factors of tDCS-functional MRI studies Ekhtiari et al. (2022); Opitz et al. (2018) combined direct intracranial measurements of efield generated by transcranial electric stimulation with modeling by SimNIBS, showing that the electrode positioning should be kept within 1 cm when tDCS is applied. In our study, two independent investigators conducted simulation of efield using the same imaging cohort and were blinded for age, sex and diagnosis. Highly consistent results between the two investigators suggest validity of the simulation technique used in our study.

The main limitation of this study is that simulation of the efield was based on the structural characteristics but without consideration of the neurophysiological reactions, such as functional communication between neurons, threshold value, or refractory period. However, relatively high correlation was previously reported between the simulated efield and the actual efield (Opitz et al., 2018). Further methodological development is required based on information of structural characteristics and functional neural connectivity for simulating efield. Moreover, further studies with several stimulation montage settings are needed in addition to anode and cathode electrodes at F3 and at F4.

In conclusion, the efield of tDCS to the prefrontal cortex was simulated in patients with MDD, BP and SCZ. The SCZ group showed significant reduction of the simulated efield strength in the bilateral frontal region, brain stem and cerebellum. No correlation was found between the reduction of simulated efield strength and global function or clinical symptoms in the SCZ group. Future research will aim to elucidate the simulated efield strength as a prognostic biological marker in tDCS treatment for psychiatric disorders.

Author's contributions

Authors Uenishi and Takahashi designed the study. Authors Yamada and Uenishi produced and organized the datasets. Author Takahashi preprocessed the data, and authors Uenishi, Takahashi, Tamaki, Yasuda and Ikeda conducted imaging data processing and visual checking. Authors Uenishi and Tamaki conducted simulation of efield. Authors Uenishi and Takahashi performed the statistical analysis. Author Uenishi wrote the first draft and author Takahashi assisted writing the paper. Authors Tsuji and Kimoto provided feedback about data analysis and interpretation. Authors Mizutani-Tiebel, Keeser and Padberg provided advice on conceptualization of the study and feedback on the manuscript. All authors contributed to and have approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available in the OSF platform (https://osf.io/56ygr/).

Declaration of Competing Interest

Author Padberg is a member of the European Scientific Advisory Board of Brainsway Inc., Jerusalem, Israel, and the International Scientific Advisory Board of Sooma, Helsinki, Finland. He has received speaker's honoraria from Mag&More GmbH, the neuroCare Group, Munich, Germany, and Brainsway Inc. His-lab has received support with equipment from neuroConn GmbH, Ilmenau, Germany, Mag&More GmbH and Brainsway Inc. Author Mizutani-Tiebel receives remuneration from neruoCare as an office worker. The other authors declare no conflict of interest in relation to this study.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2022.111547.

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