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Title: Cortical Morphology in Cannabis Use Disorder: Implications for Transcranial Direct Current Stimulation Treatment

Running title: Cortical morphology and tDCS in addiction

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Abstract

Introduction: Transcranial direct current stimulation (tDCS) has been studied as an adjunctive treatment option for substance use disorders (SUDs). Alterations in brain structure following SUD may change tDCS-induced electric field (EF) and subsequent responses. However, group-level differences between healthy controls (HC) and participants with SUDs in terms of EF and its association with cortical architecture have not yet been modeled quantitatively.

Objective: We provided a methodology for group-level analysis of computational head models (CHMs) to investigate the influence of cortical morphology metrics on EFs.

Method: Whole-brain surface-based morphology was conducted and cortical thickness, volume, and surface area were compared between participants with CUD (n=20) and age-matched HC (n=22). We also simulated EFs for bilateral tDCS over DLPFC. Effects of structural alterations on EF distribution were investigated based on individualized CHMs.

Results: In terms of EF, no significant difference was found within the prefrontal cortex. However, EFs were significantly different in left-postcentral and right-superior temporal gyrus ($P < 0.05$) with higher level of variance in CUD compared to HC ($F_{39,43}=5.31, P<0.0001, C=0.95$). We found significant differences in cortical area (caudal anterior cingulate and rostral middle frontal), thickness (lateral orbitofrontal), and volume (paracentral and fusiform) between two groups.

Conclusion: Brain morphology and tDCS-induced EFs may be changed following CUD. However, differences between CUD and HCs in EFs do not always overlap with brain areas that showed structural alterations. To sufficiently modulate stimulation targets, it should be checked if individuals with CUD need to be given different stimulation dose based on tDCS target location.

Keywords: tDCS, Individual Differences, Cortical Morphology, Computational Head Models, Dorsolateral Prefrontal Cortex, Substance Use Disorder

1. Introduction

The number of cannabis users has increased in recent years and despite its legalization in different parts of the world, concerns remain about its effects on the adolescent brain (Connor et al., 2021; Kroon, Kuhns, Hoch, & Cousijn, 2020). Although cannabis is one of the most consumed drugs in the world, there is currently no validated drug treatment and available pharmacological therapies for cannabis use disorders (CUD) have low long-term success rates (Fogaça, Galve-Roperh, Guimarães, & Campos, 2013). So, there is an urgent need to identify and develop novel therapeutic interventions for CUD. Recent advancements in human neuroscience have provided new adjuvant treatment options including noninvasive brain stimulation (NIBS) interventions for those individuals with CUD who desire to quit substance abuse based on targeting the neurocognitive processes (Kearney-Ramos & Haney, 2021; Sahlem et al., 2020).

In substance use disorders (SUDs), it has been reported that activity in the prefrontal cortex and its connectivity to the subcortical regions (including striatum and amygdala) that are related to addictive behaviors such as drug craving can be modulated by NIBS methods (Jansen et al., 2013; Ma, Sun, & Ku, 2019). Research on repetitive transcranial magnetic stimulation (rTMS) for the treatment of CUD showed encouraging results for enhancing drug craving or consumption (Kearney-Ramos & Haney, 2021; Martin-Rodriguez et al., 2021; Prashad, Dedrick, To, Vanneste, & Filbey, 2019; Sahlem, Baker, George, Malcolm, & McRae-Clark, 2018; Sahlem et al., 2020). Transcranial direct current stimulation (tDCS), as a portable and low-cost device, has also the capacity to induce remarkable effects on executive functions and addictive behaviors (Chen, Qin, He, & Zou, 2020; H. J. Kim & Kang, 2020). For example, previous investigations revealed that tDCS can affect decision-making and craving in chronic marijuana users (Boggio et al., 2010). The application of tDCS in the field of CUD attracted more attention in recent years and two ongoing clinical trials (<https://clinicaltrials.gov/>) registered in 2020 (NCT04389528) and 2021 (NCT04871048) confirm the growing interest in using tDCS as a treatment option for CUD. However, it is not clear that the dosing parameters used for previous tDCS studies (among healthy controls or other types of addiction) will be efficacious in CUD. In order to use tDCS as a treatment option for CUD, it is critical to consider unique aspects of the neurobiological effects of cannabis that might influence the efficacy of brain stimulation.

Structural cortical abnormalities have consistently been found in people with substance use disorders in general and CUD in particular (Chye et al., 2021; Chye et al., 2019; Cousijn et al., 2012; Lorenzetti, Chye, Silva, Solowij, & Roberts, 2019; Lorenzetti et al., 2020). Various factors (e.g., the types of drugs, addiction severity, and age of onset) affect the extent and location of morphological changes of the cerebral cortex. Because tDCS produces diffuse current flow, brain morphological alterations (in targeted or non-targeted brain areas) following CUD can be one of the most critical factors that may affect tDCS outcomes. For example, the efficacy of tDCS to prefrontal areas, which is commonly used as a target in brain stimulation studies, is related to underlying cortical morphology (Filmer, Ehrhardt, Shaw, Mattingley, & Dux, 2019; Suen et al., 2021). Inspired by (McCalley & Hanlon, 2021), brain structural changes in cannabis dependence can affect tDCS-induced electric field distribution patterns that might be associated with further behavioral changes in response to tDCS (J.-H. Kim et al., 2014; Laakso, Mikkonen, Koyama, Hirata, & Tanaka, 2019; Suen et al., 2021). With respect to the brain morphology alterations in CUD and the critical role of the brain structure in the efficacy of tDCS, individuals with CUD may need a different stimulation dose in order to sufficiently modulate cortical regions compared to age-matched healthy controls without CUD.

In this study, the main goal was to examine the impact of heavy cannabis use on cortical thickness, volume, and surface area in participants with CUD and age-matched healthy controls (HC) in a whole-brain approach and within common cortical tDCS targets in substance use disorders. Effects of alterations in brain structure on the electric field distribution patterns were also investigated based on individualized computational head models (CHMs). Since participants with CUD may have different cortical structure, we hypothesized that regions with different cortical morphology would be different in terms of electric field distribution patterns and it might be needed to be applied with different stimulation dose compared to HC to be able to modulate the brain in the same way.

2. Materials and Method

2.1. Participants

T1-weighted MR images were collected in a separate MRI study (Koenders et al., 2016). The data was obtained from the publicly available OpenfMRI database (<https://openfmri.org/>, accession number: ds000174). This dataset is related to a longitudinal study (T1-weighted structural MRI study at baseline and three years follow-up) and we only used baseline images. MRI scans were obtained from two groups of subjects: healthy control (HC group; $n = 22$ and age (mean $\pm$ SD) = 21.6 ± 2.45 years old) without a history of drug abuse and a group of heavy cannabis users (CB group; $n = 20$ and age (mean $\pm$ SD) = 20.5 ± 2.1 years old). Demographic information per group is available in Table 1.

Table 1. Demographic information per group (CB: heavy cannabis users, HC: healthy controls).

	CB (N = 20)	HC (N = 22)	Statistic	P-value
Gender, %male	75	64	$\chi^2(1) = 0.63$	$P = 0.43$
Age, mean years (SD)	20.5 (2.11)	21.6 (2.45)	$t = 1.45$	$P = 0.15$
CUDIT, mean (SD)	12.70 (6.59)	0.05 (0.21)	$t = 9.00$	$P < 0.001^{***}$
AUDIT	6.25 (3.35)	4.41 (3.38)	$t = 1.77$	$P = 0.08$
Cannabis use				
onset of first use, age years	14.50 (1.65)	18.46 (2.99)	$t = 4.37$	$P < 0.001^{***}$
onset regular use, age years	16.29 (2.35)	NA	NA	NA
current use, grams per week	2.78 (1.78)	NA	NA	NA
current use, days per week	4.70 (1.62)	NA	NA	NA

***: P value < 0.001

2.2. Analysis pipeline

The workflow for data extraction is illustrated in Fig.1. Our analysis method consists of two separate parts; (1) structural data processing, and (2) creation of CHMs, both based on the surface-based reconstruction of brain images. The details of data analysis are entirely described in the following sections.

Figure 1: Workflow for data analysis. T1-weighted anatomical images were collected in a separate MRI study from two groups of subjects: cannabis users (CB group; $n=20$) and healthy controls (HC group; $n=22$) [REF]. In the next step, structural MRI were analyzed in two separate lines: A) Extraction of structural characteristics; sMRIs were preprocessed in FreeSurfer, after surface reconstruction for all of the subjects each brain surface was transformed to fsaverage standard space and structural features of the brain including thickness, volume, and area were calculated at the group-level. General linear model (GLM) was used to determine between group differences in terms of cortical morphology metrics B) Electric field intensity simulations; in the second line of analysis surface-based computational head models were simulated based on the following steps: segmentation of the T-weighted images, calculation of the head volume meshes, modeling and placement of two $5 \times 7 \text{ cm}^2$ electrode pads, simulation of the bilateral tDCS montage aimed at DLPFC stimulation (anode/cathode over F3/F4 in EEG 10-20 standard system with 2 mA current intensity), calculation of finite element method, predict EF intensity distribution for each individual, and transformation of the models to the standard fsaverage space. Same as structural data, GLM was used for group-level analysis of CHMs C) Atlas-based parcellation; a surface-based anatomical atlas (Desikan-Killiani) was applied to the brain surfaces and computational head models and structural features and EF intensity were calculated in each region of the brain. D) Statistical analysis: Correlation between EFs and cortical metrics were calculated for each individual and across each group. Linear mixed effect models were used to investigate the effects of cortical metrics on induced EFs.

2.2.1. Structural data processing

For analysis of brain structure, T1-weighted MR images were processed using FreeSurfer analysis environment version 6.0, which is available freely online (<http://surfer.nmr.mgh.harvard.edu/>). Automated processing pipeline ("recon-all" with the default set of parameters), which allows surface-based three-dimensional reconstruction and quantification of cortical morphology, was used to calculate gray matter (GM) volume, surface area, and cortical thickness for each

hemisphere. Surface-based processing steps were based on previous reports (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). Briefly, Processing steps included motion correction, removal of non-brain tissue, transformation to Talairach space, intensity normalization, segmentation of sub-cortical tissues, intensity normalization, tessellation of the GM-white matter (WM) boundary, automated topology correction, and surface deformation. All reconstructions were visually inspected and manually edited as necessary to ensure proper classifications and reconstructions for all of the subjects. The reconstructed surfaces were registered to a standard surface ("fsaverage") in FreeSurfer, with a smoothing level full width half maximum (FWHM) Gaussian kernel of 10 mm to allow matching of cortical locations across subjects (Fischl et al., 1999).

Cortical thickness was measured by averaging the distance between the pial surface and the GM-WM surface (Fischl & Dale, 2000). The surface area was computed at the GM-WM boundary, as the average area of all triangles surrounding each vertex. Cortical volume was obtained by multiplying cortical area and cortical thickness vertex-by-vertex by the automated procedure for volumetric measures of the brain structures implemented in FreeSurfer. Cortical measurements aligned in standard fsaverage space were fed into the general linear model (GLM) using "mri_glmfit" to compare each structural measurement between two groups at each vertex along with the cortical mesh. Statistical maps were thresholded at $P < 0.05$ and corrected for multiple comparisons. To assess the spatial overlap of EF and structural measurements (thickness, area, and volume), significant clusters from each whole-brain analysis that survived multiple comparison corrections were combined with EFs in a conjunction map. Finally, automated cortical parcellation and region of interest (ROI) definition were performed using Desikan Killiani atlas (Fan et al., 2016) resulting in mean cortical surface area, cortical thickness, and cortical volume estimations calculated from all vertices within the atlas cortical parcellations per hemisphere.

2.2.2. Creation of computational head models

Modeling of induced EFs was performed using the standard SimNIBS 3.0 (Thielscher, Antunes, & Saturnino, 2015). In the first step, T1-weighted MR images were segmented into five tissue types, including the scalp, skull, cerebrospinal fluid (CSF), gray matter (GM), and white matter (WM). Segmentations were carefully examined slice by slice to ensure accurate segmentation of the brain tissues. Then, tetrahedral meshes were generated for each segmented tissue and

visualized using Gmsh (Geuzaine & Remacle, 2009). Two large conventional electrode pads (5x7 cm²) with 1 mm thickness were simulated. Anode/cathode electrode was placed over F3/F4 location in EEG 10-20 standard system with 2 mA current intensity. DLPFC is commonly targeted by tDCS or TMS and, in this study, we only focused on the bilateral F4/F3 DLPFC stimulation because previous systematic reviews revealed that this montage is the most frequent montage for people with SUDs (Ekhtiari et al., 2019). However, the pipeline is adaptable to other electrode montages as well. In the next step, linear electrical conductivities (σ) were assigned to each voxel based on the previously reported isotropic values (scalp: 0.465, skull: 0.010, CSF: 1.654, GM: 0.275, WM: 0.126, electrode rubber sheet: 0.1; all in Siemens/meter).

Next, a transformation was applied to the individualized head models to normalize them into a standard space. In order to do group-level analysis, the surface-based EFs were mapped into the standard average surface ("fsaverage") of the FreeSurfer using inter-subject registration procedure in SimNIBS (Fischl et al., 1999). All head models were fed into the FreeSurfer and a general linear model (GLM with "mri_glmfit") was used to evaluate the main effect of the group on EF. Resultant statistical maps were thresholded at $P < 0.05$ and corrected for multiple comparisons. In addition to whole-brain calculations, we also applied ROIs analysis based on standard parcellation of CHMs using Desikan Killiani atlas (Fan et al., 2016). The spatial mean EF, as an indicator of stimulation strength, was calculated in all ROIs obtained from atlas-based parcellation.

2.3. Association analysis

All statistical analyses were performed in R statistical software package (Team, 2013) and MATLAB. Using atlas-based parcellation, cortical measures, mean EF, and peak EF were extracted from each sub-region. Six different linear mixed effect models (LMEs) were used to indicate the relationship between the structural features (surface area, cortical thickness, and cortical volume) and EF indices (2 different measures; mean and peak). The LMEs allow us to investigate the effects of explanatory variables and their interactions (here: group, ROI, cortical measures as "fixed effects") on the dependent variable (here: EF distribution patterns) while statistically controlling for the effects of randomly selected subjects ("random effect") on the dependent variable. Multiple models were run and a likelihood-ratio test via ANOVA was used to investigate the goodness of fit of different models. Each model was "EF index = group + structural feature + structural feature*group" with a random effect for the subject.

Since we didn't find any significant role for group or group by structure interaction in LME models, we calculated the correlation between induced EFs and structural measurements in all 34 cortical parcellations per hemisphere for each group separately. For all of the statistical analyses in *R*, false discovery rate (FDR) correction was used to correct *p*-values for ignoring multiple comparisons, and $p_{\text{corrected}} < 0.05$ was considered significant.

3. Results

3.1. Extraction of structural characteristic results

The comparison of structural measurements in CB and HC groups is presented in Fig.2 and Table.2. The significant clusters in Table.1 are named based on Desikan-Killiani atlas annotation in FreeSurfer. In the left hemisphere, CB group showed significantly decreased cortical surface area in two clusters. The clusters were in the caudal anterior cingulate and rostral middle frontal. In the right hemisphere, CB group revealed significantly lower cortical thickness in one cluster. The cluster was in the lateral orbitofrontal. Based on cortical volume analysis, CB group showed significantly lower volume in two clusters, including paracentral and fusiform in the left hemisphere. These significant clusters were considered as the main ROIs for comparing induced EFs between the two groups.

Figure 2: Group-level analysis of cortical measurements. Results from whole-brain vertex-wise analysis of cortical measurements between cannabis users (CB group) compared with healthy controls (HC group) for (A) surface area (b) thickness and (C) cortical volume based on a general linear model analysis in Freesurfer. All of the results are related to HC > CB contrast. Statistical maps are depicted on the inflated surface to allow visualization sulci (dark gray) as well as gyri (light gray). Regions that remained significant following a cluster-based multiple comparison correction procedure are depicted (cluster-wise threshold, $P < 0.05$). Lower row is related to spatial overlap of regions demonstrating significant differences in EFs (illustrated in Figure 3) and significant differences in (D) surface area, and (E) cortical volume among CB group compared with HC. No spatial overlap was found between significant clusters in EF and cortical thickness.

Table 2. Descriptive report of clusters showing a significant difference ($P < 0.05$) between cannabis users (CB group) and healthy controls (HC group) on cortical measurements including surface area, thickness, and cortical volume corrected for multiple comparisons.

Brain location	Contrast	Cluster size (mm ²)	CWP (<i>P</i> value)	MNI coordinate		
				x	y	z
Surface area						
Left hemisphere						
Caudal anterior cingulate	HC > CB	3773.63	0.00260	-6.3	15.5	30.7
Rostral middle frontal	HC > CB	3673.80	0.00320	-31.0	46.1	16.0
Thickness						
Right hemisphere						
Lateral orbitofrontal	HC > CB	1379.18	0.01594	33.7	29.2	-15.7
Volume						
Left hemisphere						
Paracentral	HC > CB	1635.61	0.00898	-15.5	-43.1	69.2
Fusiform	HC > CB	1463.91	0.01851	-34.3	-13.7	-31.8

3.2. Creation of CHMs results

In the second line of our analysis, surface-based CHMs were simulated for all 42 participants ($n = 22$ for HC group, $n = 20$ for CB group). At the group-level analysis of CHMs, the average and standard deviation (SD) of the absolute EFs are shown for each group in Fig.3. Bilateral DLPFC stimulation induced higher EFs in CB group (global maximum values range from 0.34 to 0.95 V/m) compared to HC (global maximum values range from 0.34 to 0.59 V/m). Furthermore, standard deviation of the EF intensity in CB group is higher than HC that can be considered as an indicator of higher inter-individual variability among the participants of CB group.

Fig.3.b depicts results from the whole-brain analysis comparing EFs between CB group and HC. Clusters in this figure surviving multiple comparison corrections. As mentioned in Table.3, significant clusters were found in the left (CB> HC: fusiform, temporal pole, supramarginal, lateral occipital, and parahippocampal middle temporal; HC> CB: superior frontal and postcentral) and right (CB> HC: lateral occipital, inferior temporal, inferior parietal, middle temporal, parahippocampal, fusiform, inferior parietal, and superior temporal) hemispheres. These significant clusters were considered as the main ROIs for finding the correlations between induced EFs and cortical metrics. The size (in mm²) of each cluster and Montreal Neurological Institute (MNI) coordinate for the location of maximum significance (z-score) are reported in Table.3. The results are reported based on Freesurfer's automatically labeled parcellation scheme defining temporal, parietal, and occipital cortices separately.

Figure 3: a. Within group variance. Average and standard deviation (SD) of the EF intensity in volt per meter [V/m] for cannabis users (CB group) and healthy controls (HC group) in standard fsaverage space with bilateral DLPFC stimulation (anode/cathode over F3/F4 with 2 mA current intensity). b. Between group differences. Results from whole-brain vertex-wise analysis of electric fields between cannabis users (CB group) compared with healthy controls (HC group) for (A) CB > HC and (b) HC > CB based on a general linear model analysis in Freesurfer. Statistical maps are depicted on the inflated surface to allow visualization sulci (dark gray) as well as gyri (light gray). Regions that remained significant following a cluster-based multiple comparison correction procedure are depicted (cluster-wise threshold, $P < 0.05$).

Table 3. Descriptive report of clusters showing a significant difference ($P < 0.05$) between cannabis users (CB group) and healthy controls (HC group) on EF distribution patterns corrected for multiple comparisons.

Brain location	Contrast	Cluster size (mm ²)	CWP (<i>P</i> value)	MNI coordinate		
				x	y	z
Left hemisphere						
Fusiform	CB > HC	5491.47	0.00020	-32.7	-34.3	-24.7
Temporal pole	CB > HC	447.92	0.00020	-29.0	9.0	-38.8
Supramarginal	CB > HC	365.47	0.00140	-53.6	-52.5	23.7
Lateral occipital	CB > HC	290.04	0.00092	-13.9	-95.3	-12.8
Para hippocampal	CB > HC	280.70	0.01157	-24.0	-28.5	-22.9
Middle temporal	CB > HC	243.05	0.03076	-56.4	-22.6	-21.0
Superior frontal	HC > CB	489.97	0.00020	-6.5	9.3	62.9
Postcentral	HC > CB	302.92	0.00679	-43.1	-7.8	14.4
Superior frontal	HC > CB	289.22	0.00918	-8.6	26.9	36.2
Right hemisphere						
Lateral occipital	CB > HC	3624.41	0.00020	22.5	-95.8	-12.9
Inferior temporal	CB > HC	977.74	0.00020	50.5	-36.6	-23.9
Inferior parietal	CB > HC	604.83	0.00020	40.6	-67.8	26.1
Middle temporal	CB > HC	591.15	0.00020	49.6	-57.9	1.4
Para hippocampal	CB > HC	369.51	0.00040	17.8	-37.9	-8.2
Fusiform	CB > HC	355.97	0.00080	35.0	-3.7	-39.6
Inferior parietal	CB > HC	315.60	0.00380	48.4	-60.2	25.6
Superior temporal	CB > HC	292.74	0.00898	46.5	11.0	-22.6

3.3. Association results

In five ROIs (paracentral, fusiform, caudal anterior cingulate, and rostral middle frontal in the left hemisphere, and lateral orbitofrontal in the right hemisphere) obtained from the morphological analysis (reported in Table.2), the difference between the two groups was calculated in terms of averaged EFs. We found that, in the left fusiform, mean EF in CB group (0.0725 ± 0.01) was significantly ($P = 0.0091$) higher than HC group (0.0662 ± 0.01). However, no significant difference was found in other clusters.

As mentioned in Table.4, LME models showed no main effects of group or group by structure interaction for both mean and peak EFs. However, we found the main effects for all of the structural measurements ($p < 0.001$) in peak EF estimation and the main effect of thickness in mean EF calculations ($p < 0.001$).

Table 4. Results of six linear mixed effects models after applying atlas parcellation to determine the role of group, structural, interaction of group by structure as predictors, subjects as intercept and mean EF and peak EF as two separate dependent variables.

<i>Predictors</i>	<i>Mean EF</i>			<i>Peak EF</i>		
	<i>Estimates</i>	<i>CI</i>	<i>P</i>	<i>Estimates</i>	<i>CI</i>	<i>P</i>
Model 1						
Intercept	0.13	0.12 – 0.13	<0.001	0.20	0.18 – 0.22	<0.001
Group	-0.00	-0.01 – 0.01	0.543	-0.01	-0.03 – 0.02	0.465
Area	-0.00	-0.02 – 0.02	0.803	0.11	0.07 – 0.14	<0.001
Group*Area	0.01	-0.02 – 0.03	0.718	-0.03	-0.07 – 0.02	0.252
Model 2						
Intercept	0.12	0.12 – 0.13	<0.001	0.19	0.17 – 0.21	<0.001
Group	-0.00	-0.01 – 0.01	0.641	-0.01	-0.03 – 0.02	0.563
Volume	0.01	-0.00 – 0.01	0.171	0.05	0.04 – 0.07	<0.001
Group*Volume	0.00	-0.01 – 0.01	0.905	-0.01	-0.03 – 0.00	0.121
Model 3						
Intercept	0.06	0.03 – 0.08	<0.001	0.12	0.07 – 0.16	<0.001
Group	0.01	-0.02 – 0.04	0.528	0.01	-0.05 – 0.06	0.864
Thickness	0.03	0.02 – 0.04	<0.001	0.04	0.03 – 0.06	<0.001
Group*Thickness	-0.00	-0.02 – 0.01	0.430	-0.01	-0.03 – 0.01	0.442

After parcellation of the CHMs based on the Desikan-killiani atlas, the mean and peak EFs were extracted from each region. The correlation between induced EFs (mean or peak) and each structural characteristic (surface area, cortical thickness, or cortical volume) was also calculated at the ROI level. Our calculations showed a significant correlation between mean EF and cortical thickness in the left superior frontal gyrus ($R = 0.7$, $p = 0.044$) in CB group. Nonetheless, in HC group, we found more significant correlations between brain features and induced EFs. Our results demonstrated that the correlations between mean EF and cortical thickness were significant in the left ($R = 0.73$, $p = 0.008$) and right ($R = 0.65$, $p = 0.033$) frontal pole. Furthermore, correlations between peak EFs and cortical thickness were significant in the left ($R = 0.63$, $p = 0.042$) and right frontal pole ($R = 0.7$, $p = 0.018$). The correlation between cortical volume and EFs showed a significant correlation with mean EF in the left frontal pole ($R = 0.78$, $p = 0.001$) only in the HC group.

4. Discussion

This investigation examining brain morphology and tDCS-induced electric field (EF) differences between healthy controls (HCs) and a group of participants with substance use disorders (SUDs) yielded four main results. First, we found that CB group showed the lower surface area in the left caudal anterior cingulate and left rostral middle frontal gyrus, lower cortical thickness in right lateral orbitofrontal, and lower cortical volume in the paracentral and fusiform gyrus in the left hemisphere. Second, we found the greatest averaged EF in the frontal pole and highest maximum EF in the superior frontal gyrus with more significant inter-individual variability among heavy cannabis users (CB group) compared to healthy controls (HC group). Third, averaged EF in the fusiform gyrus was significantly different between two groups. However, we found no main effects of group and group by structure interaction on induced EFs (mean or peak). Finally, we found that the in bilateral DLPFC stimulation frontal pole received the highest EF across the brain that showed significant correlations between induced EFs and brain structure.

Conforming with the previous modeling studies, our simulation results showed inter-individual variability within both HC and CB groups in terms of EF intensity due to individual brain anatomy (Laakso, Tanaka, Koyama, De Santis, & Hirata, 2015; Laakso et al., 2016; Opitz, Paulus, Will, Antunes, & Thielscher, 2015) with greater standard deviation (SD) in CB group (Fig.2). The higher SD among heavy cannabis users can be considered as an indirect indicator of more variability in brain structure compared to healthy subjects (Lorenzetti et al., 2019). Populations with SUDs are highly variable from person to person, and different parameters including clinical characteristics like the history of polydrug abuse, biological factors like person's genetic background, and psychological aspects related to the person's unique history and personality during lifetime may affect brain alterations resulting from substance use (Abuse, US, & General, 2016). Higher inter-individual variations across participants in CB group emphasize the importance of individualized treatment plans to tailor tDCS as a therapeutic method in addiction medicine.

Our simulations, in line with previous computational modeling studies, revealed that bilateral electrode montage (Nasseri, Nitsche, & Ekhtiari, 2015) can be a suitable electrode configuration for modulating DLPFC. However, given the diffusivity of the brain current flow produced by conventional tDCS and interaction between different brain regions, it would be challenging to explain causality between a targeted brain region (e.g., DLPFC in this study) and stimulation

outcomes (Kuo et al., 2013). For instance, we found that, in addition to DLPFC, the orbitofrontal cortex (OFC), as a part of the prefrontal cortex, also received high EFs in bilateral stimulation of DLPFC. OFC is implicated in emotional/motivational executive functions (Fuster, 2001) and has specific connections with subcortical associative learning nodes such as the basolateral amygdala and nucleus accumbens. (Chudasama & Robbins, 2006). OFC generally contributes to monitoring reward values assigned to different choices and clinical studies have revealed that this region is involved in disorders and behaviors accompanied by risky decision-making and impulsivity like drug addiction (Volkow & Fowler, 2000). A recent functional MRI research, by applying repetitive transcranial magnetic stimulation (rTMS) for nicotine-dependent participants, suggested that anti-craving effects of DLPFC stimulation might be related to decreased activity in medial OFC and nucleus accumbens (Li et al., 2017). Therefore, the diffusivity of the current and the probability of interaction between targeted and non-targeted regions, and whole-brain structural alterations should be considered in interpreting the stimulation outcomes in clinical populations. High definition (Datta et al., 2009; Edwards et al., 2013) or multifocal tDCS targeting (Fischer et al., 2017) deliver a more focal stimulation and avoid spreading the current over non-targeted brain regions, however, have not yet been used for SUDs.

The whole-brain calculation for comparing two groups of subjects that is used in this study might be more effective than local comparison in pre-defined ROIs. Whole-brain group-level vertex-wise analysis of CHMs to find between-group differences has not been examined in previous tDCS modeling studies. Consistent with our first hypothesis, we found that CB group demonstrated different EF intensity compared with HC group based on our GLM approach for CHMS. However, significant clusters obtained from group-level analysis of CHMs were not located in prefrontal cortices as targeted brain areas. Generally speaking, between-group differences in EFs may be helpful to explain inconsistent behavioral outcomes since it has been reported that current flow in a cortical target can predict response to tDCS (Datta et al., 2009; J.-H. Kim et al., 2014; Laakso et al., 2019). For example, different effects of tDCS on cognitive performance in subjects with SUDs compared with healthy controls that were examined in previously published studies may be related to different EF patterns. For instance, Boggio and his colleagues in (Boggio et al., 2010) reported that anodal stimulation over DLPFC of heavy marijuana users and healthy controls lead to increased risk-taking behavior in cannabis users compared with healthy participants. However, the relationship between behavioral outcomes and induced EFs was not investigated. Hopefully, the

between-group analysis of CHMs can help find a better answer for between-group variation in the behavioral response to tDCS.

Based on the GLM analyses of morphological metrics, our results were in line with some previous researches. Here, we found a significant difference between CB and HC groups in the right lateral OFC regarding cortical thickness with lower thickness in CB group. In particular, the right lateral part of the OFC has been implicated in inhibitory processes that suppress previously rewarded choices (Elliott & Deakin, 2005; Elliott, Dolan, & Frith, 2000). Right lateral OFC produces anticipatory responses about upcoming decisions based on integrating prior outcome information with current perceptual details (Nogueira et al., 2017). Levar et al. compared cannabis users with non-users and found a significant main effect of group on the lateral OFC thickness (Levar, Francis, Smith, Ho, & Gilman, 2018). In another study, a group of marijuana users was compared with non-user participants. There were some trends towards cortical thickness differences in OFC between groups with lower thickness in marijuana users (Mashhoon, Sava, Sneider, Nickerson, & Silveri, 2015). However, in general terms, there is a lack of consistency in the effects of SUDs on brain structure measurements. For example, no group difference in cortical thickness in cannabis use disorders (Mata et al., 2010), or thicker cortex in different regions in the frontal, parietal, temporal, and occipital lobe was reported previously on the effects of cannabis use (Jacobus et al., 2015; Lopez-Larson et al., 2011).

Our CB group showed a smaller surface area in caudal anterior cingulate and rostral middle frontal. These findings are consistent with previous results showing that cannabis use disorder is associated with marginally decreased surface area in the medial and ventral lateral prefrontal cortex (Shollenbarger, Price, Wieser, & Lisdahl, 2015). We also found a significant cluster in caudal anterior cingulate when we compared the surface area between the two groups. The smaller surface area in the caudal anterior cingulate cortex in CB group may be related to the loss of inhibitory control over the use of cannabis. Yet, our results are inconsistent with prior findings demonstrating no differences between cannabis users and controls (Mata et al., 2010) or significant differences in cuneus surface area (Sullivan, Wallace, Wade, Swartz, & Lisdahl, 2020). These variations in the effects of SUDs on brain structure in existing literature might be due to some factors like the differing number of subjects in previous studies that may affect statistically significant results, age of samples or analysis design including whole brain or predefined ROIs analyses.

Here, we found lower cortical volume in the left paracentral and fusiform gyrus in CB group. These brain regions were investigated in few numbers of previous studies and marijuana users showed lower density in the parietal lobe and higher density around fusiform gyrus (Matochik, Eldreth, Cadet, & Bolla, 2005). These regions have been implicated in cognitive processes particularly in attention and working memory (Kirchhoff, Wagner, Maril, & Stern, 2000) and may be related to functional deficits in cannabis users (Bolla, Brown, Eldreth, Tate, & Cadet, 2002). A previous fMRI drug cue-reactivity study reported that specific clusters in occipital, limbic, cerebellum and temporal regions, including fusiform had greater activation during cannabis cues than neutral images. However, fusiform was the only region that showed a significant negative correlation between its activation and craving score. It suggested that this brain region that has a role in visual salience might be involved in cue-induced craving (Charboneau et al., 2013).

Despite significant differences in brain structural measurements that we have found between two groups, we did not find a main effect of group or group by structure (surface area, thickness, or volume) interaction on averaged or peak EFs. This reveals that induced EFs and distribution of the injected current through the brain were not significantly influenced by structural alterations associated with SUDs. When looking at the areas that were significantly different between two groups in terms of brain structural measurements (including paracentral, fusiform, caudal anterior cingulate, rostral middle frontal in the hemisphere, and lateral OFC in the right hemisphere), we found a subtle difference between two groups in averaged EFs only in the fusiform gyrus. This region is a part of the temporal lobe and is not intentionally targeted in bilateral DLPFC stimulation and other brain regions showed no significant differences between the two groups. While we found similar patterns of the EF distribution between two groups, it is still unclear whether this similarity can be interpreted as the same tDCS-related effects in both groups. More details of functional or behavioral information are needed to determine differences between the two groups in response to tDCS.

Our findings based on a whole-brain parcellation approach to finding the association between EF and structural measurements in each ROI revealed that correlations between mean/peak EFs and cortical structure were significant in the bilateral frontal pole in HC group and left superior frontal gyrus in CB group. Based on these findings, no significant associations were found in other brain regions. On the other hand, parcellation of CHMs at the group level showed that frontal pole and

superior frontal gyrus were strongly stimulated so that the highest averaged and peak EFs were found in these two regions. Therefore, it seems that by increasing induced EF intensity, the importance of brain structure will be increased. Our findings suggest that EFs are associated with brain structural measurements such as thickness or volume in strongly stimulated brain areas. Structural differences between the two groups should be considered, especially in these brain regions.

5. Limitation and future directions

We are aware that our research may have several limitations. The first is that our results are restricted to structural information of the brain. Behavioral or functional effects of tDCS were not available in our dataset, and we couldn't assess the relationship between EF intensity, brain structure, and clinical or functional responses to tDCS. However, there is tremendous consensus across the labs on tDCS modeling workflow with key features set since 2009 (Datta et al., 2009). modeling studies were validated repeatedly in previous in-vivo, in-vitro, and in-silico studies based on human or animal brains. For example, intracranial recordings of brain current flow from 10 living subjects were correlated with subject-specific current flow models (Huang et al., 2017). Independently, intracranial recordings from patients, cadavers, and non-human primates confirm insights from computational head models (Opitz et al., 2016; Underwood, 2016). Indeed, significant engineering effort has been directed toward finite element modeling and reported that these models can accurately predict the distinct voltage distribution over the scalp which is correlated with the current flow through the cortex (Datta, Zhou, Su, Parra, & Bikson, 2013). Different imaging techniques were also used to detect magnetic fields induced by tDCS currents in post mortem individuals (Antal et al., 2014) or healthy subjects (Jog et al., 2016). With respect to the validity of head models, CHMs are commonly used to individualize stimulation dose account for vulnerable populations (Kessler et al., 2013; Shekhawat & Vanneste, 2018; Truong, Magerowski, Blackburn, Bikson, & Alonso-Alonso, 2013).

Next, we used automatic tissue segmentation and outcomes are strongly dependent on the quality of the T1-weighted images and segmentation algorithm. More precise segmentation algorithms especially for the creation of the head models can be investigated in future studies. Furthermore, our dataset did not enable evaluating diffusion tensor imaging (DTI) to consider tissue anisotropy. We have assumed isotropic conductivity, as is common in computational modeling studies. Using

previously established electrical conductivity might affect EF distribution patterns, especially in the skull and WM (Opitz, Windhoff, Heidemann, Turner, & Thielscher, 2011; Suh, Lee, & Kim, 2012). However, anisotropic conductivity is necessary when EF in deeper parts of the brain is considered (Wagner et al., 2013). Another limitation is that our simulations are focused on EF intensity induced by conventional bilateral tDCS over DLPFC. We ignored the radial component of the EF, which is informative of EF direction. The normal component of the EF reflects current either entering (anodal effect) or leaving the cortex (cathodal effect) may be instructive in between-group comparisons.

There are still many questions to be answered in future studies. One of the main remaining questions is whether induced EFs in targeted or non-targeted brain areas are associated with other neuroimaging information such as fMRI data. Future research is needed to incorporate head models and fMRI data more comprehensively to help design tES-fMRI protocols more accurately, especially in clinical applications. Our pipeline can be used to integrate CHMs with additional neuroimaging information and behavioral outcomes that may shed new light on the sources within/between-group variation in response to tDCS in future works. Furthermore, fundamental questions remain regarding the optimal electrode configuration. Concerning the importance of individualizing stimulation protocols, more simulations are needed to determine personalized electrode montage based on a person's cortical morphology. For example, the ideal montage for subjects with SUDs should be based on a patient-tailored approach that considers different aspects related to alterations in brain structure, and the clinical implication of these montages should be explored in future studies.

6. Conclusion

In summary, to the best of our knowledge, this is the first study that compares cannabis users with healthy controls for implications of tDCS treatment in a whole-brain approach. Results from this study reveal that: (1) CUD-induced morphological changes may occur in brain regions relevant to tDCS targets (like orbitofrontal cortex), (2) group-level differences in EF distribution patterns in bilateral stimulation of DLPFC can be found in some non-targeted areas (far from DLPFC as the main target), (3) group-level differences between CUD and HCs in terms of tDCS-induced EFs do not always overlap with the brain areas obtained from group-level differences in the structural measures, (4) more variance and less significant correlations were found between EF and cortical

metrics in cannabis group compared to healthy subjects that emphasize more inter-individual variability among clinical populations. The proposed pipeline in this study can be used to integrate CHMs with other neuroimaging information, including functional MRI data. Pursuing this direction while accounting for cortical morphology, and other possible confounding such as functional brain activity, neuropsychiatric background, and so on, hopefully, provides insights into the mechanisms behind inter-individual variability in response to non-invasive brain stimulation technologies.

Conflict of interest

The authors have no conflict of interest to disclose.

Author contribution

GS, and HE designed the study. GS performed simulations and data analysis under HE and FT supervision. GS wrote the paper with input from HE, MS, and FT. All authors (GS, FT, MS, and HE) contributed to manuscript preparation and interpretation of data. All authors agreed on the final manuscript before submission.

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