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Computational Simulation of Transcranial Magnetic Stimulation-Induced Electric Fields in the Dorsolateral Prefrontal Cortex of Heavy Cannabis Using Individuals

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Abstract

We aimed to investigate the influence of demographic and clinical modulators on the strength of transcranial magnetic stimulation (TMS)-induced electric fields (EFs) in the left dorsolateral prefrontal cortex (lDLPFC) in heavy cannabis using individuals. Structural T1-weighted magnetic resonance imaging scans of 20 heavy cannabis using individuals and 22 non-cannabis users (the controls) in the age range of 18-25 were retrieved. Computational simulations of TMS-induced EFs in the lDLPFC were performed. No significant difference in the strength of TMS-induced EFs was observed between heavy cannabis using individuals and the controls. A negative correlation between the scalp-to-cortex distance demonstrated and the strength of the induced EFs. The severity of cannabis use related problems did not correlate with the induced EFs in the lDLPFC of heavy cannabis using individuals. However, the severity of alcohol use related problems was negatively correlated with the induced EF in the lDLPFC localized by the 5-cm method in the whole sample. Early adulthood seems related to an increase in the induced EFs in the lDLPFC. In conclusion, the dominant factor influencing TMS-induced EFs was the scalp-to-cortex distance. In early adulthood, the interaction between age and comorbid substance use may influence with the magnitude of TMS-induced EFs, thereby complicating the treatment effect of TMS in young people with substance use disorders.

1. Introduction

In the context of substance use disorders, excitatory transcranial magnetic stimulation (TMS) over the left dorsolateral prefrontal cortex (lDLPFC) has been proven to be an effective therapeutic option (Zhang et al., 2019). Understanding the impact of various factors on the responsiveness to TMS is crucial for achieving a precise and individualized neuromodulation therapy for substance use disorders (Cocchi and Zalesky, 2018). It remains controversial whether demographic factors affect brain responses to TMS. Brain atrophy is associated with an increase in the scalp-to-cortex distance (SCD), which is an important variable that affects the strength of TMS-induced electric fields (EF) in elderly patients with Alzheimer's disease (Lu et al., 2019). However, the effect of SCD on TMS-induced EFs in young adults with substance use disorders is still unknown. Sex is another factor that may affect brain responses to TMS. A recent simulation demonstrated that females received a stronger TMS-induced EF over the frontopolar region than males (Hanlon and McCalley, 2022). Additional clinical evidence supports the sex difference in mediating the antidepressant effects of TMS (Sackeim et al., 2020). However, whether the sex has an impact on the effect of TMS on the lDLPFC in people with substance use disorders also remains unknown. In addition to demographic factors, the influence of the severity of substance use related problems and years of substance use on TMS-induced EF remains unexplored.

We therefore performed computational simulations of TMS-induced EF in the brains of heavy cannabis using individuals, to compare the strength of TMS-induced EFs in the lDLPFC in heavy cannabis using individuals with non-cannabis users (Objective 1), and to explore the influence of demographic and clinical factors on the strength of TMS-induced EFs in the lDLPFC in both groups (Objective 2).

2. Material and Method

2.1 Sample characteristics

This simulation study was conducted based on a sample of T1-weighted magnetic resonance imaging (MRI) scans of 20 heavy cannabis using individuals (mean age=20.53±2.11) and 22 non-cannabis users (mean age=21.56±2.45), in the age range of 18-25. The data were drawn from the OpenNeuro repository. The scanning parameters were described previously (Cousijn et al., 2014; Cousijn et al., 2012; Koenders et al., 2016). The severity of cannabis use related problems was measured using the Cannabis Use Disorder Identification Test (CUDIT). The severity of alcohol use related problems was another parameter considered, which was measured using the Alcohol Use Disorder Identification Test (AUDIT). Heavy cannabis using individuals were defined as those who had used cannabis for at least two years for more than 10

days per month. Non-cannabis users (the controls) did not consume cannabis at the time of the study had not used cannabis one year prior the study and had used cannabis on fewer than 50 occasions in their lifetime (Cousijn et al., 2014; Koenders et al., 2016).

2.2 Computational simulation

SimNIBS version 4.0 was used for computational simulations (Thielscher et al., 2015). Three commonly used methods for localizing the lDLPFC were applied: (1) the 5-cm method (MNI coordinates: -41, 16, 54) (Fox et al., 2012), (2) the Beam F3 method (MNI coordinates: -40.6, 41.7, 34.3) (Trapp et al., 2020) and (3) the MRI navigator-based method (MNI coordinates: -38, 44, 26) (Zhang et al., 2023). The stimulation intensity during the simulations was set to 10%, 30%, 50%, 70%, and 90% of the maximal machine output of the stimulator. The strength of the TMS-induced EF was computed as the vector norm of the induced EF (Thielscher et al., 2011). Each region of interest (ROI) in the individual space was transformed from its MNI coordinates, and the average EF in a 5-mm radius sphere in each model was subsequently extracted (Zhang et al., 2023). The technical details can be found in the **supplement.**

2.3 Statistical analysis

Demographic and clinical factors were compared between groups using the independent t-test or Fisher's exact test. Two-way analysis of covariance (ANCOVA) was performed to study the influence of group and stimulation intensity on the strength of TMS-induced EF, with the scores of CUDIT and AUDIT included as covariates. In the regression analysis, we only included the induced EF at 50% of machine output (MO) as the dependent variable, because the simulated TMS-induced EF was scaled accordingly to the level of MO. First, a univariate analysis of demographic/clinical factors and the strength of TMS-induced EFs was conducted for the purposeful selection of variables. In the analysis of the full sample, age, sex, group (cannabis users/non-cannabis users), AUDIT, and SCD were possible predictors in the model. In the analysis of the sample of heavy cannabis using individuals, age, sex, years of frequent cannabis use, CUDIT, AUDIT, and SCD were included as possible predictors. Second, independent variables that showed a trend toward significance (p<0.10) or statistical significance (p<0.05) were included in the subsequent multivariate regression model with backward elimination (Haque et al., 2018). A less restrictive level of 0.1 was used in the univariate regression to identify a wide range of explanatory variables that could potentially be linked to the dependent variable in the multivariate regression model (Lang, 2007). A separate regression analyses on the full sample and heavy cannabis users was performed.

3. Results

There were no significant differences in age, sex, SCD, or AUDIT between cannabis-addicted individuals and the controls (Table 1). At each stimulation intensity, no significant difference in the strength of TMS-induced EFs was observed between heavy cannabis using individuals and the non-cannabis controls (all intensity-by-group interactions>0.05 in ANCOVA analysis; Figure 1A).

3.1 Full sample analysis

We first identified SCD, AUDIT, and gender as significant predictors in the univariate analyses. Subsequently, multivariate regression analysis showed that AUDIT scores and SCD were significant predictors of TMS-induced EF strength over the lDLPFC localized using the 5-cm and navigator-based methods, while age and SCD were significant predictors of TMS-induced EF strength over the lDLPFC localized using the Beam F3 method (Table 2).

3.2 Analysis of heavy cannabis using individuals

Initially, SCD, years of frequent cannabis use, and age were found as significant predictors in the univariate analyses. Subsequently, multivariate regression analysis showed that SCD was a significant predictor of TMS-induced EFs in the lDLPFC localized using all three methods. Additionally, age was found to be a significant predictor of TMS-induced EFs in the lDLPFC, localized using the navigator-based method (Table 2).

4. Discussion

Our findings indicate that SCD was the dominant factor influencing TMS-induced EFs in the lDLPFC. Age was correlated with the strength of the induced EFs, possibly implying maturation of the adolescent brain. Heavy cannabis use disorders and sex did not significantly influence TMS-induced EFs. The severity of alcohol use related problems was correlate with the strength of TMS-induced EFs, indicating that different substance use disorders may result in varied responses to TMS-induced EFs.

Consistent with previous simulations on dementia and Parkinson's disease (Lu et al., 2019; Lu et al., 2023), SCD was the determining factor for TMS-induced EFs. We did not observe a significant difference in SCD over the lDLPFC between young heavy cannabis using individuals and the non-cannabis controls, suggesting that TMS can induce comparable strength of EFs in young heavy cannabis using individuals compared to non-cannabis users. Age was correlated with the strength of TMS-induced EFs, possibly implying the ongoing maturation of the brain in early adulthood in the

age range of 18-25. Interestingly, the severity of alcohol use related problems, but not of cannabis use related problems, correlated with the strength of EFs over the lDLPFC localized using the 5-cm method. Research evidence suggests that people with alcohol use disorders receive a weak EF over the frontopolar region because of increased SCD (McCalley et al., 2023). However, our study suggests that the influence of alcohol use related problems on TMS-induced EFs in the lDLPFC is independent of SCD.

The current study cannot rule out the impact of heavy cannabis use on strength of TMS-induced EFs in heavy cannabis users due to several reasons. First, it is possible that the maturation process of the early adult brain may have compensated for some of the deficits observed in the TMS-induced EFs. Second, it is worth noting that, among the non-cannabis controls, the majority (21 out of 22 cases) exhibited AUDIT scores >1 and 5 out of 22 cases have AUDIT scores≥8. The scores indicate the presence of low-to-potentially harmful levels of alcohol consumption in the controls. Therefore, between-group difference in the TMS-induced EFs might be partially obscured by alcohol-related brain changes in both groups. Third, the original MRI study found a significant impact of heavy cannabis use on some subcortical areas, but not on the lDLPFC (Cousijn et al., 2012). Structural impairment in the subcortical regions could influence the networking effects of TMS targeting the lDLPFC (Mitra et al., 2023); however, the networking effects of TMS is challenging to be explored using simulations. Lastly, the fact that the controls included individuals who have used cannabis, but not heavily, may introduce biases in the current findings.

Conclusion

The dominant factor influencing TMS-induced EFs was the SCD. In early adulthood, the interaction between age and comorbid substance use may influence with the magnitude of TMS-induced EFs, thus complicating the treatment effect of TMS in cannabis addiction. To account for variability in TMS-induced EFs attributed to individual characteristics, we emphasize the need of using individualized computational modeling in TMS planning for addiction treatment, which would help optimize dosage and ultimately lead to a more robust clinical efficacy. To confirm the findings from our simulations, future study may explore the real-world clinical efficacy of TMS in cannabis use disorder treatment and address any potential confounding factors that may influence its effects.

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Declaration of conflicting interests

None.

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Author contributions

JZ: Conceptualization, Data curation, Data analysis, Visualization, Writing – original draft.
ZB: Data curation, Writing – review
JC, DV and KF: Writing – review

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Figure legend

Figure 1. (A) Simulation of the strength of TMS-induced electric fields (EF) in the three regions of interest (ROIs). MO: machine output. (B) Correlation between SCD and TMS-induced EFs in the lDLPFC localized using three methods. SCD: Scalp-to-cortex distance. (C) Correlation between AUDIT scores and TMS-induced EF in the left DLPFC localized using the 5-cm method. AUDIT: Alcohol Use Disorders Identification Test. lDLPFC: Left dorsolateral prefrontal cortex.

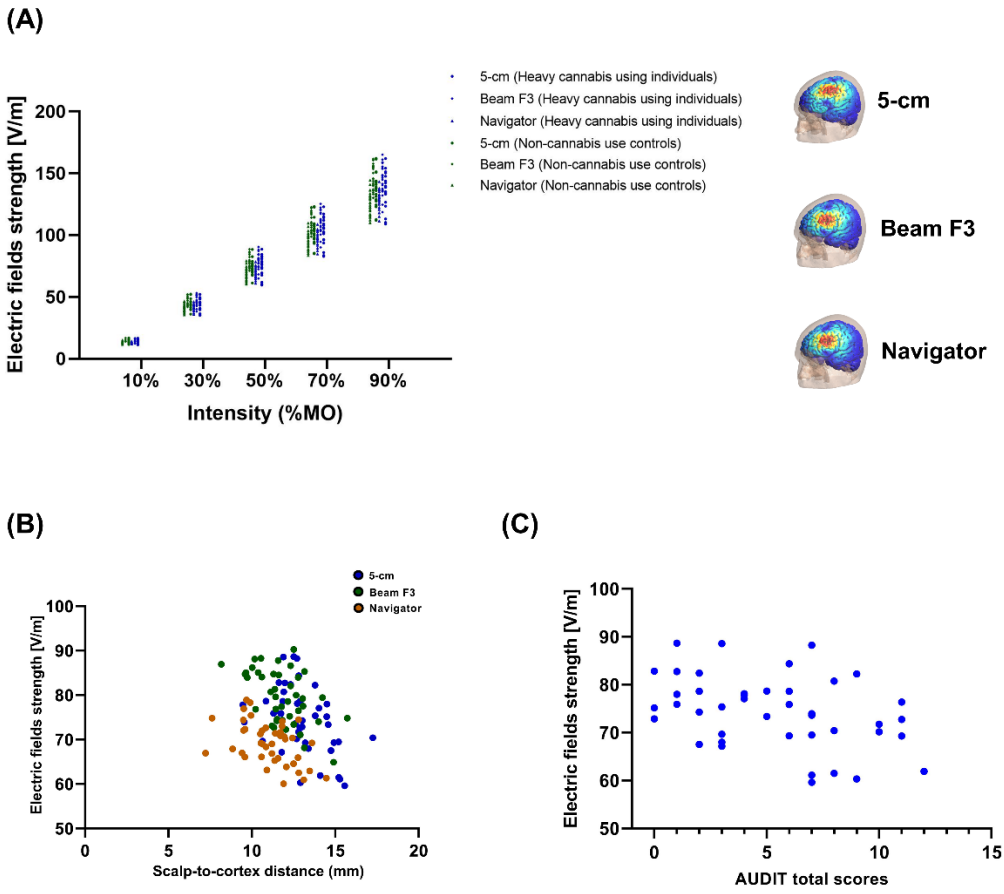
(A)
Electric fields strength [V/m]
200
150
100
50
0
10%
30%
50%
70%
90%
Intensity (%MO)
5-cm (Heavy cannabis using individuals)
Beam F3 (Heavy cannabis using individuals)
Navigator (Heavy cannabis using individuals)
5-cm (Non-cannabis use controls)
Beam F3 (Non-cannabis use controls)
Navigator (Non-cannabis use controls)
5-cm
Beam F3
Navigator
(B)
5-cm
Beam F3
Navigator
Electric fields strength [V/m]
100
90
80
70
60
50
0
5
10
15
20
Scalp-to-cortex distance (mm)
(C)
Electric fields strength [V/m]
100
90
80
70
60
50
0
5
10
15
AUDIT total scores

Figure 1.

Table 1. Summary of sample characteristics

	Heavy cannabis using individuals (n=20)	Non-cannabis use controls (n=22)	*p*
Age (years)	20.53 (2.11)	21.56 (2.45)	0.154[a]
Sex (Male/Female)	15/5	14/8	0.514[b]
CUDIT scores	12.70 (6.59)	0 (0)	
Years of frequent cannabis use (years)	4.33 (2.48)	/	
AUDIT scores	6.25 (3.35)	4.41 (3.38)	0.084[a]
SCD at the left DLFPC (mm, the 5-cm method)	12.81 (1.77)	13.19 (1.50)	0.445[a]
SCD at the left DLFPC (mm, the Beam F3 method)	11.85 (1.45)	11.81 (1.56)	0.935[a]
SCD at the left DLFPC (mm, the navigator-based method)	10.95 (1.71)	11.21 (1.42)	0.590[a]

Abbreviations: CUDIT: Cannabis Use Disorder Identification Test; AUDIT: Alcohol Use Disorder Identification Test; SCD: Scalp-to-cortex distance; DLPFC: Dorsolateral prefrontal cortex.

[a]Independent-t test; [b]Fisher's exact test

Table 2. Summary of regression analyses

	Full sample (n=42)					Heavy cannabis using individuals (n=20)			
	B	**SE**	**β**	***p***		**B**	**SE**	**β**	***p***
The 5-cm method					**The 5-cm method**				
Univariate regression					*Univariate regression*				
SCD	-0.830	0.318	-0.382	**0.013**	SCD	-2.391	0.900	-0.531	**0.016**
AUDIT	-2.037	0.657	-0.440	**0.004**	AUDIT	-0.850	0.523	-0.358	0.121
Sex	4.863	2.420	0.303	**0.051**	CUDIT	-0.026	0.285	-0.022	0.927
Group	0.875	2.346	0.059	0.711	Sex	8.844	3.677	0.493	**0.027**
Age	0.165	0.511	0.051	0.749	Age	0.335	0.888	0.089	0.710
Multivariate regression					Years since frequent cannabis use	0.662	0.740	0.206	0.383
SCD	-1.819	0.628	-0.393	**0.006**	*Multivariate regression*				
AUDIT	-0.706	0.295	-0.325	**0.022**	SCD	-2.391	0.900	-0.531	**0.016**
The Beam F3 method					**The Beam F3 method**				
Univariate regression					*Univariate regression*				
SCD	-2.105	0.551	-0.517	**<0.001**	SCD	-2.996	0.854	-0.637	**0.003**
AUDIT	0.083	0.277	0.047	0.767	AUDIT	0.177	0.476	0.087	0.715
Sex	-0.894	2.041	-0.069	0.664	CUDIT	-0.147	0.241	-0.143	0.549
Group	0.759	1.890	0.063	0.690	Sex	-1.333	3.597	-0.087	0.715
Age	0.867	0.389	0.332	**0.031**	Age	0.981	0.726	0.304	0.193
Multivariate regression					Years since frequent	0.817	0.617	0.298	0.202

					cannabis use				
Age	0.865	0.329	0.332	**0.012**	*Multivariate regression*				
SCD	-2.104	0.514	-0.517	**<0.001**	SCD	-2.996	0.854	-0.637	**0.003**
Navigator-based method					**Navigator-based method**				
Univariate regression					*Univariate regression*				
SCD	-1.383	0.431	-0.452	**0.003**	SCD	-1.086	0.556	-0.418	**0.067**
AUDIT	0.305	0.212	0.222	0.157	AUDIT	0.225	0.308	0.170	0.474
Sex	-0.009	1.601	-0.001	0.995	CUDIT	-0.017	0.159	-0.025	0.916
Group	-0.650	1.479	-0.069	0.662	Sex	-0.598	2.354	-0.060	0.802
Age	0.305	0.319	0.150	0.344	Age	1.022	0.435	0.484	**0.030**
Multivariate regression					Years since frequent cannabis use	0.848	0.372	0.474	**0.035**
SCD	-1.383	0.431	-0.452	**0.003**	*Multivariate regression*				
					SCD	-1.363	0.453	-0.524	**0.008**
					Age	1.225	0.368	0.580	**0.004**

Abbreviations: CUDIT: Cannabis Use Disorder Identification Test; AUDIT: Alcohol Use Disorder Identification Test; SCD: Scalp-to-cortex distance; DLPFC: Dorsolateral prefrontal cortex.

The *p*-values less than 0.1 were highlighted in bold.