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# Modulation of dopaminergic transmission and brain activity by frontotemporal tDCS: A multimodal PET-MR imaging study

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ABSTRACT

*Background:* Transcranial Direct Current Stimulation (tDCS) is a promising noninvasive intervention for schizophrenia, particularly when applied using a frontotemporal montage. Although significant clinical benefits have been reported, the variability in individual responses underscores the need for a more comprehensive understanding of its underlying neurophysiological mechanisms. Here, we used a simultaneous positron emission tomography (PET) and magnetic resonance imaging (MRI) approach (PET-MR) to investigate the effects of frontotemporal tDCS on dopamine transmission, cerebral perfusion, and white matter microstructural integrity in healthy individuals.

*Methods:* In a double-blind, two-arm, parallel group study, 30 healthy volunteers were randomly allocated to receive a single session of either active (n = 15) or sham (n = 15) frontotemporal tDCS. The stimulation session was delivered during simultaneous multimodal PET-MR imaging, which combined PET with the [$^{11}$C]raclopride radiotracer, Arterial Spin Labeling (ASL), and Diffusion Weighted Imaging.

*Results:* PET [$^{11}$C]raclopride analysis revealed a significant reduction in Non-Displaceable Binding Potential in the left executive striatal subregion 15 min after tDCS in the active group, compared to both baseline and the sham group. This finding suggests that frontotemporal tDCS may induce an increase in dopamine release. ASL analysis showed that active tDCS may reduce cerebral blood flow in the precuneus compared to sham stimulation. No significant effects of tDCS were observed on white matter microstructural integrity.

*Conclusion:* This study provides new insights into the neurophysiological mechanisms of frontotemporal tDCS, paving the way for the optimization of therapeutic strategies for patients with dysregulated cortico-subcortical dopamine systems.

## 1. Introduction

Transcranial Direct Current Stimulation (tDCS) is a noninvasive brain stimulation technique that allows modulation of a targeted brain network in living humans. tDCS consists of delivering a weak electrical current through at least two electrodes placed over the scalp of a participant to modulate brain activity and connectivity of the targeted brain regions. tDCS has been shown to enhance cognitive functions in healthy individuals [1,2]. In addition, tDCS has been increasingly used as a therapeutic for patients with various psychiatric and neurological conditions, with different electrode montages being explored [3,4]. In particular, tDCS has emerged as a promising intervention for treatment-resistant schizophrenia, where conventional treatments often have limited efficacy. The most common electrode arrangement for this indication involves placing the anode over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the left temporoparietal junction (TPJ) [5]. These regions are targeted because their activity and functional connectivity are disrupted in schizophrenia [6,7], with

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additional evidence of microstructural integrity abnormalities in the white matter tracts connecting these areas [8,9]. The frontotemporal tDCS montage has shown promising clinical results for both negative symptoms [10] and hallucinations [11] in patients with schizophrenia. However, while some patients respond fully to repeated sessions of tDCS others show little to no clinical improvement. In addition, the precise neurophysiological mechanisms underlying the effects of frontotemporal tDCS remain to be fully elucidated. A better understanding of these mechanisms is crucial to optimize its therapeutic application in schizophrenia.

In this context, some studies have investigated the neurophysiological effects of frontotemporal tDCS using MRI techniques, such as fMRI, in patients with schizophrenia. For instance, repeated sessions of frontotemporal tDCS increased the resting-state functional connectivity of the left TPJ with the left DLPFC, the left angular gyrus and the precuneus, while decreasing it with the left anterior insula and the right inferior frontal gyrus [12]. Notably, the decrease in left TPJ-insula connectivity correlated with the reduction in hallucinations. Other studies have sought to understand the variability in clinical response by using MRI-based modeling approaches to predict the distribution of tDCS-induced currents. Clinical response has been associated with the strength of the tDCS-induced electric field reaching specific brain regions, such as the left transverse temporal gyrus [13]. Moreover, modeling approaches have revealed that electric fields induced by frontotemporal tDCS are not confined to the left frontotemporal network but also reach deeper brain structures, such as the basal ganglia. This suggests that frontotemporal tDCS may modulate the broader dopaminergic network, potentially influencing its function [14].

Schizophrenia is intricately associated with abnormal activity and functional connectivity, as well as disrupted white matter integrity within corticostriatal networks [15,16], alongside abnormal dopamine transmission [17]. Neuroimaging studies have shown that the altered frontal and temporal regions targeted by frontotemporal tDCS are closely linked to dopamine networks [18]. Pharmacological evidence has highlighted two key points: (1) antipsychotics that effectively address both negative and positive symptoms of schizophrenia primarily function as dopamine antagonists, and (2) pro-dopaminergic agents have the potential to induce psychotic-like symptoms. Interestingly, in a recent study in healthy volunteers, we reported that bifrontal tDCS with anodal stimulation over the left DLPFC and cathodal stimulation over the right DLPFC induced a release of dopamine in the ventral striatum [19]. Altogether, these results emphasize the importance of investigating the effects of frontotemporal tDCS on dopamine release, as well as on the activity and integrity of dopaminergic networks, to better understand and optimize its therapeutic potential in schizophrenia.

The current study aims to elucidate the neurophysiological effects of a single session of frontotemporal tDCS using a simultaneous multimodal imaging approach (PET-MR) in healthy volunteers. The online implementation of the stimulation will allow deciphering changes induced during and after stimulation. The distributed changes will be explored at rest through: 1) specific and localized dopaminergic transmission, evaluated by positron emission tomography (PET) with [$^{11}$C] raclopride binding to assess dopaminergic D2 subtype receptor availability in the striatum and its functional subdivisions; 2) brain activity measured quantitatively by cerebral blood flow (CBF) using arterial spin labelling (ASL); and 3) white matter microstructural integrity, assessed by diffusion weighted imaging (DWI). While previous studies have reported some of the neurophysiological effects of tDCS with other montages [19,20], including its effects on white matter microstructural integrity [21,22], there is limited knowledge regarding its impact when using a frontotemporal montage. We hypothesized that frontotemporal tDCS would modulate dopaminergic transmission, brain activity and white matter microstructural integrity in dopamine-related networks during and after stimulation, compared to sham. This investigation aimed to provide insights into the underlying mechanisms of frontotemporal tDCS and its potential therapeutic implications.

## 2. Materials and methods

### 2.1. Experimental design

This study used a randomized, double-blind, two-arm, parallel group design, with participants receiving either active (n = 15) or sham (n = 15) frontotemporal tDCS. Each participant underwent a single 3-h experimental visit at the CERMEP imaging center (Lyon, France). During this visit, participants received a single tDCS session while undergoing a multimodal PET-MR scan protocol. The scan included an anatomical MRI (T1) followed by a simultaneous PET acquisition with two DWI acquisitions (pre- and post-stimulation) and three ASL acquisitions (pre-, during, and post-stimulation) (Fig. 1).

### 2.2. Participants

Thirty-seven healthy adults were recruited. Seven were excluded due to technical issues, leaving a final analyzed sample of 30 participants (mean age = 25.67 ± 2.57 years, 15 females). Inclusion criteria included being aged 18–30 years and right-handed. Exclusion criteria included a history of neurological, psychiatric or addictive disorders (including tobacco smoking) assessed during a structured interview with a psychiatrist, family history of psychiatric disorders (first degree), current medication (except oral contraceptives), contraindications to MRI/tDCS, and pregnancy. Participants were asked to abstain from caffeine and intense physical exercise on the day of scanning. The study, approved by an ethics committee (CPP Sud Est 3 2015-064 B on November 2, 2015; ANSM 2015-A01281-48) and pre-registered on ClinicalTrials.gov (NCT03056170), adhered to the Declaration of Helsinki, with written informed consent given by all participants and monetary compensation provided (100€). Participants completed personality questionnaires, including the Life Orientation Test-Revised (LOT-R) that assesses dispositional optimism [23], the global motivation scale [24], and the Big Five Inventory (French version [25]). Psychometric and sociodemographic characteristics are presented in Table 1.

### 2.3. Data acquisition

Imaging was performed at the CERMEP Imaging Center (Lyon, France) using a Biograph mMR PET-MR system (Siemens), which allowed simultaneous PET and MR acquisition. PET imaging assessed dopamine transmission using [$^{11}$C]raclopride, while MR imaging included anatomical T1-weighted scans, ASL for cerebral blood flow, and DWI for microstructural white matter integrity (Fig. 1). Detailed imaging parameters, including sequence settings and reconstruction methods, are provided in the **Supplementary Material**.

### 2.4. Transcranial Direct Current Stimulation

tDCS was administered using an MR-compatible device (NeuroConn DC-Stimulator Plus MR, Ilmenau, Germany). As proposed for schizophrenia [11], the anode was placed at the midpoint between F3 and FP1 (left DLPFC) and the cathode at the midpoint between T3 and P3 (left TPJ), according to the international 10/20 EEG electrode placement system (Fig. 1). Electrodes (7 × 5 cm$^2$) were applied to the participant's scalp using conductive paste (Ten20) before entering the scanner. Active stimulation was set at 1 mA and delivered for 30 min with a 30-s ramp up/down. For the sham condition, the device's built-in sham mode was used, delivering 1 min of active tDCS (30-s ramp up/down) at the start to replicate the initial tingling sensation and mimic the sensory artifacts of active tDCS. Stimulation began 40 min after the [$^{11}$C]raclopride injection and lasted for 30 min.

Participants completed a questionnaire on tDCS adverse effects [26] before and after the scan. The integrity of blinding was assessed by having participants guess whether they received active or sham

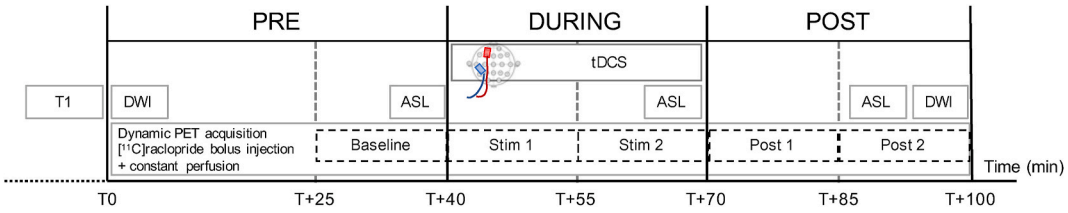


**Fig. 1. Experimental design of the study combining simultaneous multimodal PET-MR imaging and frontotemporal tDCS.** During a single experimental visit, participants underwent a 30-min session of frontotemporal tDCS (anode in red over the left dorsolateral prefrontal cortex and cathode in blue over the left temporoparietal junction) while simultaneously undergoing a multimodal PET-MR scan. The scan included PET acquisition (with [$^{11}$C]raclopride to assess dopamine transmission), anatomical MRI (T1-weighted), two diffusion-weighted (DWI) acquisitions (before and after tDCS) to assess white matter microstructure integrity, and three arterial spin labeling (ASL) acquisitions (before, during, and after tDCS) to measure cerebral blood flow as an indirect index of brain activity.

**Table 1**
Participant Characteristics in the Active and Sham tDCS Groups.

| | Active tDCS (N = 15) | Sham tDCS (N = 15) | p value |
|---|---|---|---|
| ***Demographic and psychometric*** | | | |
| Age (years) | 25.00 (2.07) | 26.13 (2.94) | 0.233 |
| Sex (Male/Female) | 5/10 | 10/5 | 0.144 |
| Motivation score | 128.53 (17.08) | 125.93 (20.17) | 0.706 |
| LOT-R score | 15.33 (3.96) | 17.33 (4.27) | 0.194 |
| BFI Neuroticism score | 20.66 (6.59) | 17.06 (5.62) | 0.119 |
| ***tDCS*** | | | |
| Impedance | 13.66 (1.11) | 13.63 (0.77) | 0.940 |
| Tingling sensation (Yes/No) | 7/8 | 8/7 | 1.000 |
| Blinding (Active/None/Sham) | 6/4/5 | 7/6/2 | 0.414 |
| ***PET*** | | | |
| Injected dose (MBq/kg) | 4.77 (0.58) | 4.31 (0.80) | 0.083 |

Note: Data are presented as mean (standard deviation) for continuous variables and N for categorical variables. Group differences were assessed using Student's t-test for continuous variables and chi-square tests (with continuity correction) for categorical variables.
Abbreviations: BFI, Big Five Inventory; LOT-R, Life Orientation Test-Revised; N, Number; tDCS, transcranial Direct Current Stimulation.

stimulation.

### 2.5. Data processing and analysis

All preprocessing steps were carried out by a single individual blind to group allocation. Details for each step are provided in the **Supplementary material-Methods**.

#### 2.5.1. Anatomical segmentation

T1-weighted MRI images were rigidly coregistered to the mean PET image for each participant and then spatially normalized into standard MNI space. Striatum regions of interest (ROIs) were obtained from the Oxford-GSK-Imanova connectivity striatal atlas [27], which divides striatum according to cortical-striatal anatomical connections into limbic (connected to the orbitofrontal cortex and the anterior cingulate), executive (connected to the DLPFC) and sensorimotor (connected to sensorimotor cortical regions) subregions (Fig. 2). Specifically, the executive (associative) striatum comprises the dorsal caudate and anterior putamen, the limbic striatum includes the nucleus accumbens (Nacc), ventral caudate, and ventral putamen, and the sensorimotor striatum corresponds to the posterior putamen. A reference anatomical ROI, the cerebellum (without vermis), was obtained from the Hammersmith maximum probability brain atlas [28] and used as a reference region due to its low density of specific dopamine D2-like receptors [29]. As a supplementary analysis, anatomical region of interest (ROI) subregions of the striatum — including the NAcc, putamen, and caudate — were also examined using the Hammersmith maximum probability brain atlas (see Supplemental Material Table 3).

#### 2.5.2. PET kinetic modelling

To assess the free and nonspecific [$^{11}$C]raclopride ligand kinetics, time-activity curves (TACs) were extracted for striatal and cerebellar ROIs [29]. Distribution volume ratio (DVR) of [$^{11}$C]raclopride was computed with the multiple-time Logan graphical method with reference region [30] using the *logan* function of the Turku PET library. DVR represents the ratio of specific (ROI) to non-specific (REF) binding of the radiotracer in tissue. The Logan plots were drawn and controlled visually for linearity and quality of the data. From regional PET TACs, DVR

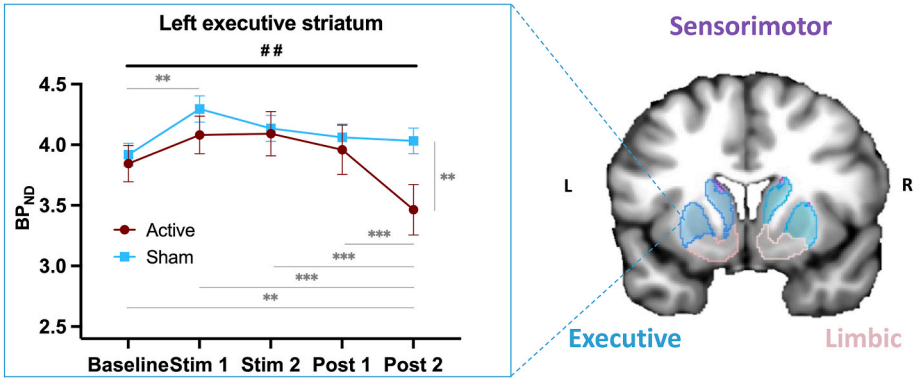


**Fig. 2. Changes in [$^{11}$C] raclopride non-displaceable Binding Potential ($BP_{ND}$) in the left executive striatum during and after frontotemporal tDCS in the active and sham groups.** The curves show the variation in $BP_{ND}$ across five time points: Baseline (25–40min), Stim1 (40–55min), Stim2 (55–70min), Post1 (70–85min) and Post2 (85–100min) for the active group (red line) and the sham group (blue line). A significant decrease in $BP_{ND}$, indicating dopamine release, is observed at Post2 in the active compared with the sham group. Error bars represent the standard error of the mean. # indicates significant Group by Time interaction; * indicates significant post hoc differences. Executive, limbic, and sensorimotor striatal subregions are illustrated for reference as defined by the Oxford-GSK-Imanova connectivity striatal atlas.

was computed for five time-intervals (Fig. 1): Baseline (25–40min), Stim1 (40–55min), Stim2 (55–70min), Post1 (70–85min) and Post2 (85–100min). DVR of each interval is the average of three data points. Values below or above three times the interquartile range were considered outliers and removed from analysis. From DVR, the non-displaceable binding potential ($BP_{ND}$), specifically quantifying the binding of the radiotracer to its target [31], was computed by subtracting 1 from the DVR. Raw $BP_{ND}$ values were computed for each functional subregion of the striatum (i.e., limbic, executive and sensorimotor) for each time interval (Baseline, Stim1, Stim2, Post1 and Post2).

#### 2.5.3. ASL

ASL preprocessing consisted in motion correction, coregistration of T1 and perfusion-weighted images, segmentation, creation of subject-specific brain masks, denoising and smoothing (see **supplementary material**). CBF maps were quantified for each participant and acquisition (pre-, during, post-stimulation), corrected for partial volume effects and normalized into MNI space.

#### 2.5.4. DWI preprocessing and tract-based spatial statistics (TBSS) analysis

Image processing included distortion, head motion and eddy currents correction, merging of the three DWI repetitions into a single 4D-volume comprising one B0 and 30 direction volumes, brain extraction, diffusion tensor and Fractional Anisotropy (FA)-maps estimation (see **supplementary material**). Data were prepared for statistical analysis using TBSS in FSL [32]. Individual FA maps were non-linearly aligned and registered to the standard Montreal Neurological Institute (MNI) space (FNIRT), resampled to an isotropic 1 mm resolution. A mean FA skeleton was created using a FA threshold of 0.2 to restrict the analysis to white matter tracts and each participant's aligned FA maps were projected onto this skeleton.

### 2.6. Statistical analyses

Sociodemographic and psychometric characteristics were analyzed using JASP (version 0.19). Group differences (active vs. sham tDCS) were assessed using independent t-tests for continuous variables and chi-squared tests for categorical variables. Statistical significance was set at $p < 0.05$.

#### 2.6.1. [11C]raclopride $BP_{ND}$

Regional $BP_{ND}$ variation were analyzed using JASP (version 0.19) with a repeated-measure analysis of variance (ANOVA) for each subregion of the striatum, with time interval as the within-subject factor and group as the between-subject factor. In case of a significant interaction between time and group, post-hoc tests were conducted and considered significant at $p < 0.05$, with Bonferroni correction applied for multiple comparisons. Effect sizes were reported as partial eta squared ($\eta_p^2$) for ANOVA and Cohen's *d* for post-hoc tests.

#### 2.6.2. ASL CBF analyses

CBF maps was analyzed using SPM12 with a flexible factorial design based on repeated measure ANOVA comparing active and sham tDCS across three time periods: Pre-stimulation (30–36min), during stimulation (60–66min) and Post-stimulation (91–97min). This analysis was done using a whole brain mask (Hammersmith maximum probability brain atlas). Contrasts included: $[(\text{During - Pre})_{\text{sham}}$ vs $(\text{During - Pre})_{\text{active}}]$, $[(\text{Post - Pre})_{\text{sham}}$ vs $(\text{Post - Pre})_{\text{active}}]$, $[(\text{Post - During})_{\text{sham}}$ vs $(\text{Post - During})_{\text{active}}]$. Statistical maps were thresholded at $P_{uncorr} < 0.001$ at the voxel level, with a minimum cluster size of 69 contiguous voxels, based on the expected number of voxels per cluster in the 3D Gaussian space. Clusters were considered significant if they survived family-wise error (FWE) correction at $P_{FWE} < 0.05$ at the cluster level. Significant clusters were identified using the Hammersmith atlas. Supplementary exploratory analyses were performed on additional ROIs under electrodes location (left DLPC and left TPJ).

#### 2.6.3. DWI FA analysis

Whole-brain mean FA skeleton were compared between active and sham tDCS ($[(\text{Pre-Post})_{\text{sham}}$ vs $(\text{Pre-Post})_{\text{active}}]$ contrast) using FSL Randomize Tool with non-parametric permutation tests [33]. Threshold-free cluster enhancement (TFCE) was applied for multiple comparisons, with significance set at $p < 0.05$ [34]. Supplementary exploratory analyses were performed on additional ROIs.

### 2.7. Data and code availability

The data and custom-written analysis code that support the findings of this study will be available on request from the corresponding author.

## 3. Results

### 3.1. Participants' characteristics

The participants' characteristics (mean and standard deviation) are shown in Table 1. No statistically significant differences were observed between the active and sham groups. No adverse effects were reported due to the tDCS stimulation, MR, or PET scans.

### 3.2. PET [11C]raclopride BPND analysis

For the left executive functional subregion of the striatum, the ANOVA revealed a significant interaction between group and time ($F_{(4,104)} = 4.367$, $p = 0.003$; $\eta_p^2 = 0.144$; Fig. 2), a significant main effect of time ($F_{(4,104)} = 11.787$, $p < 0.001$, $\eta_p^2 = 0.312$), but no significant main effect of group ($F_{(1,26)} = 1.130$, $p = 0.298$, $\eta_p^2 = 0.042$).

Intergroup post-hoc tests showed a significant difference for the Post2 period ($p_{bonf} = 0.010$, $d = -1.023$). No significant differences were found for the Stim1, Stim2, and Post1 periods.

In the active group, intragroup post-hoc tests revealed a significant 9.89 % reduction in $BP_{ND}$ in the Post2 period compared to Baseline ($p_{bonf} = 0.004$, $d = 0.684$). A significant reduction in $BP_{ND}$ was also observed when comparing the Post2 period to Stim1 ($p_{bonf} < 0.001$, $d = 1.110$), Stim2 ($p_{bonf} < 0.001$, $d = 1.130$), and Post1 ($p_{bonf} < 0.001$, $d = 0.891$) periods. No significant changes in $BP_{ND}$ were observed during the stimulation (Stim1, Stim2), or Post1 periods.

In the sham group, intragroup post-hoc analyses revealed a significant increase in $BP_{ND}$ during the Stim1 period compared to Baseline ($p_{bonf} = 0.004$, $d = -0.681$), but no significant changes in later periods.

Further ANOVA analyses of the other striatal subregions (see Supplementary Table 1), as well as the anatomical striatal subregions (nucleus accumbens, putamen, caudate; see Supplementary Table 3), revealed no significant interactions between group and time. Given that sex differences can influence dopamine binding in [$^{11}$C]raclopride PET studies, analyses including sex as an additional factor are provided in the Supplementary Table 2; however, these analyses did not change the main findings.

### 3.3. ASL CBF whole brain analysis

A significant decrease in CBF was observed in the bilateral superior parietal gyrus in the active group (−17.29 % ± 13.49) compared to the sham group (21.42 % ± 34.13) when comparing the pre- and post-stimulation periods $[(\text{Post-Pre})_{\text{sham}}$ vs $(\text{Post-Pre})_{\text{active}}]$ (Table 2, Fig. 3). A similar decrease was observed in the right superior parietal gyrus in the active group (−12.91 % ± 17.49) compared to sham group (26.49 % ± 33.62) when comparing the post-stimulation period with the period during stimulation $[(\text{Post-During})_{\text{sham}}$ vs $(\text{Post-During})_{\text{active}}]$. No significant intergroup differences were observed between the during and pre-stimulation periods $[(\text{During-Pre})_{\text{sham}}$ vs $(\text{During-Pre})_{\text{active}}]$. Furthermore, no significant clusters of increased CBF (corresponding to the

**Table 2**
Whole-Brain Analysis of CBF Changes measured by ASL in Response to Active vs. Sham frontotemporal tDCS.

| Contrast | Brain region | MNI coordinates (mm) | | | Z-score | Cluster | |
|---|---|---|---|---|---|---|---|
| | | x | y | z | | $P_{FWE}$ | k |
| ***Sham > Active*** | | | | | | | |
| **Post - Pre** | | | | | | | |
| | Superior Parietal Gyrus | 0 | −72 | 42 | 4.20 | 0.004 | 894 |
| | | 2 | −62 | 42 | 3.87 | | |
| | | −26 | −48 | 44 | 3.83 | | |
| | | 18 | −64 | 46 | 3.89 | 0.404 | 136 |
| | | 30 | −58 | 50 | 3.37 | | |
| **Post - During** | | | | | | | |
| | Superior Parietal Gyrus | 14 | −72 | 42 | 4.26 | 0.039 | 490 |

Note: Effect of tDCS on CBF were assessed in the whole brain using a flexible factorial design (time periods*groups). Clusters were considered significant with $P_{uncorr} < 0.001$ and $k > 69$ contiguous voxels (3988 $mm^3$) at the voxel level and with multiple comparisons ($P_{FWE}$)<0.05 at the cluster level. Z-scores are reported at the peak level, the $P_{FWE}$ at the cluster level and the number of contiguous voxels (k). The clusters reported here are from the contrast [Sham tDCS > Active tDCS]. No significant clusters were reported with the contrast [Sham tDCS < Active tDCS]. No significant clusters were reported for the (During stimulation – Pre) contrast.

contrast [Sham tDCS < Active tDCS]) were reported for any time period.

In addition, to address the direct tDCS modulation effects in ROI directly underneath the electrodes, a linear mixed-effects model was fitted to examine the effects of Group (active vs. sham), ROIs (left DLPFC vs. left TPJ), and Timepoint (pre-stimulation, stimulation, post-stimulation) on CBF, with random intercepts for Subject to account for repeated measures. The model revealed no significant main effect of Group ($\beta = -8.50$, SE = 9.32, t(70) = −0.91, p = .365), ROI ($\beta = -1.05$, SE = 6.39, t(140) = −0.16, p = .870), or Timepoint (e.g., stimulation vs. baseline: $\beta = -12.33$, SE = 6.39, t(140) = −1.93, p = .056). The Group × ROI × Timepoint interaction was also not significant ($\beta = -5.97$, SE = 12.78, t(140) = −0.47, p = .641), nor were any two-way interactions. The results of this supplementary analysis are presented in the Supplementary Fig. 1.

We conducted additional analyses to explore correlation between cerebral blood flow decrease in the precuneus cluster (ASL) and dopamine increase in the left executive striatum (PET) during the Post-Pre stimulation period (Supplementary Fig. 2). No significant correlation was found (Spearman; Active Group: R = −0.014, p = 0.96; Sham Group: R = 0.17, p = 0.54).

### 3.4. DWI FA analysis

No significant differences between the active and sham groups were observed in whole-brain FA maps when comparing the pre- and post-stimulation periods [$(Pre\text{-}Post)_{sham}$ vs $(Pre\text{-}Post)_{active}$].

Additional ROI analyses were conducted by extracting FA values in both the superior parietal lobule (SPL) and the striatum. Linear mixed models were used to assess the effects of Group (Active vs. Sham) and Timepoint (Pre vs. Post), with Subject included as a random effect. No significant effects were observed in either region following tDCS stimulation. In the SPL, there were no significant main effects of Group (F(1,27.37) = 0.508, p = 0.616) or Timepoint (F(1,24) = −0.721, p = 0.478), and the Group × Timepoint interaction was not significant (F(1,24) = 0.077, p = 0.939). Similarly, in the striatum, no significant main effects were found for Group (F(1,29.38) = 0.803, p = 0.429) or Timepoint (F(1,24) = 0.402, p = 0.691), nor for their interaction (F(1,24) = −0.387, p = 0.702). These findings are presented in Supplementary Fig. 3.

## 4. Discussion

This study investigated the neurophysiological effects of a single session of frontotemporal tDCS (1 mA, 30 min) in healthy volunteers using multimodal imaging. Specifically, we explored whether frontotemporal tDCS modulates dopaminergic transmission, brain activity, and white matter microstructural integrity during and after stimulation. This is crucial for understanding its therapeutic potential in neurological and psychiatric conditions involving abnormal dopamine transmission, such as schizophrenia.

[$^{11}$C]raclopride PET findings demonstrated a significant decrease in the availability of dopamine D2 receptors in the left executive striatum during the 15 to 30-min period following active frontotemporal tDCS compared to sham, suggesting an increase in extracellular dopamine in

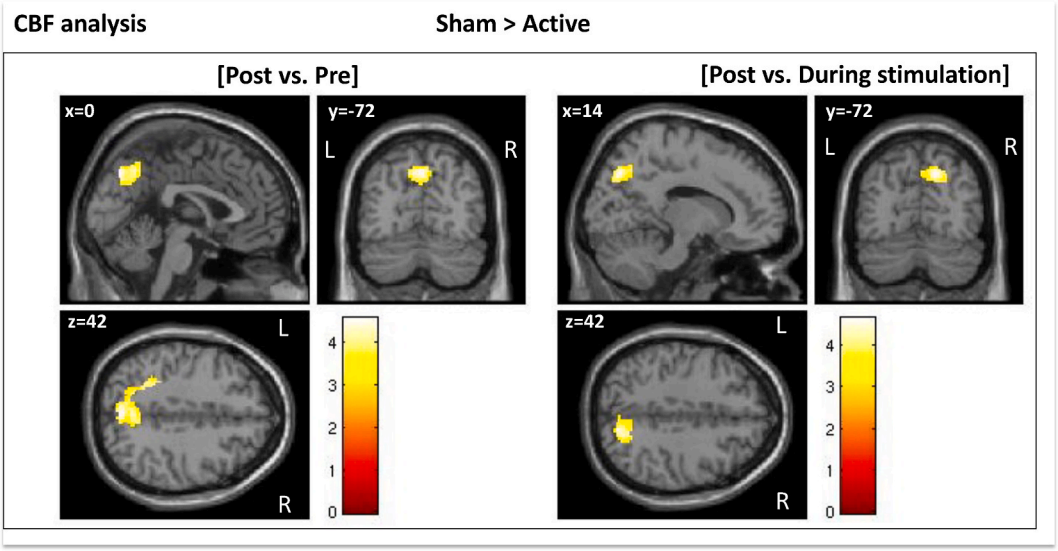


**Fig. 3. Whole brain analysis comparing CBF changes during and after frontotemporal tDCS between active (N=15) and sham (N=15) groups.** Regions of decreased CBF in the active group compared to sham when comparing the post-to the pre-stimulation period (Left), and when comparing the post-stimulation period to the period during stimulation (Right). Significant clusters were identified with $P_{uncorr} < 0.001$ and $k > 69$ contiguous voxels (3988 $mm^3$) at the voxel level and $P_{FWE}$ <0.05 at the cluster level. No significant changes were reported during stimulation compared to pre-stimulation. L, Left; R, Right.

this region. These findings are consistent with prior studies on NIBS and dopamine transmission, conducted in animal models, healthy individuals, and clinical populations [35,36]. For instance, repetitive high frequency TMS over the left DLPFC has been shown to increase extracellular dopamine in the left dorsal caudate nucleus in healthy volunteers [37] and in the striatum in patients with major depression [38]. Our results are also consistent with our previous findings of online tDCS-induced modulation of dopamine transmission in healthy individuals with a bifrontal montage [19]. Further supporting our findings, repetitive intermittent theta burst stimulation over the left DLPFC in patients with schizophrenia has been associated with reductions of negative symptoms, increased functional connectivity between the DLPFC and dopamine-associated regions [39], and dopamine release in the ventral striatum [40]. Altogether, these findings suggest that targeting the left DLPFC with either high frequency rTMS or anodal tDCS, regardless of the position of the cathode, can induce dopamine release in the striatum, indicating shared mechanisms between anodal tDCS and high frequency rTMS.

The localized modulation in the executive striatum, rather than its classical anatomical subdivisions, aligns with the organization of striato-thalamo-cortical circuits, which integrate distinct cortical and striatal regions to support complex, goal-directed behaviors [18,27,41]. The executive subdivision of the striatum, which encompasses the ventral rostral putamen, the dorsal caudate, and the superior ventral striatum, is anatomically and functionally connected to the DLPFC [27]. These strong connections between the executive striatum and the DLPFC suggests that the observed effects on dopaminergic transmission may primarily result from the stimulation of the DLPFC by our frontotemporal tDCS montage. Supporting this hypothesis, the striatal region affected in our study corresponds to the area previously identified following bifrontal tDCS targeting the DLPFC, though the effects in that case were significant only in the right hemisphere [19]. However, the stimulation of the TPJ may also contribute to these effects. Located at the intersection of the posterior temporal sulcus, inferior parietal lobule and lateral occipital cortex, the TPJ is functionally linked to subcortical structures such as the striatum, notably through its involvement in resting-state networks [42]. Through these functional connections, frontotemporal tDCS with the cathode located over the left TPJ could indirectly modulate striatal dopaminergic activity. In addition, animal studies have reported increased dopamine concentration in the striatum of rats following cathodal tDCS compared to sham and anodal conditions, with significant effects observed from 120 min after stimulation [43].

These findings have implications for understanding schizophrenia pathophysiology and the effects of tDCS in this condition. The frontotemporal tDCS montage was specifically developed to alleviate auditory hallucinations [11], targeting regions implicated in the auditory hallucination-related brain network [6]. Studies have reported increased functional connectivity between the TPJ and striatal regions in patients with auditory hallucinations (e.g. [44–47]), potentially contributing to aberrant salience processes that disrupt sensory integration [48]. Additionally, hippocampal hyperactivity, potentially driven by stress, has been implicated in the increased firing of dopaminergic neurons in the ventral tegmental area. This hyperactivity is thought to contribute to a hyper-responsive dopaminergic system in schizophrenia, a dysregulation that may be further exacerbated by a hypoactive dopaminergic tonic tone system. [49]. Although this may appear contradictory to our findings of increased dopamine in the executive striatum following frontotemporal tDCS, several hypotheses may reconcile this apparent discrepancy. First, it is important to note that frontotemporal tDCS require repeated sessions to achieve clinical effects. In our study, we only investigated the immediate effects of a single session of frontotemporal tDCS in healthy individuals without ongoing medication. Repeated tDCS sessions could potentially engage adaptive downstream mechanisms, such as changes in dopamine receptor expression or neurotrophic factor-mediated plasticity [50,51]. Second, the observed increase in dopamine could reflect changes in tonic versus phasic dopamine signaling modes, potentially mediated by the recruitment of D2 autoreceptors [17,52,53]. Such changes may decrease the hyper-reactive state seen in patients with schizophrenia, ultimately reducing symptom severity. Moreover, clinical studies often combine frontotemporal tDCS with antipsychotic medication, which may enhance its efficacy. For instance, a recent study suggested that the affinity of antipsychotic drugs for dopamine receptors can predict the clinical effects of tDCS, with high-affinity medications being associated with less symptom improvement when combined with tDCS, compared to lower-affinity medication [54]. Also suggesting an interaction between dopamine tone and tDCS effects in schizophrenia, a significant interaction was highlighted between the reduction of hallucinations following tDCS and catechol-o-methyltransferase (COMT) transferase polymorphisms in patients with schizophrenia, with a larger efficacy of tDCS in Val/Val homozygous patients [55]. In healthy individuals, the administration of dopaminergic agonists or antagonists has been reported to impact differently the after-effect of tDCS [56–60]. Finally, the dopamine release observed here may contribute to improvements in cognitive rather than positive symptoms of schizophrenia, which have also been reported following frontotemporal tDCS [11]. The reduction of positive symptoms could, instead, result from changes in other brain regions or networks. In summary, while our findings highlight acute dopaminergic effects of frontotemporal tDCS in healthy individuals, their translation to schizophrenia requires further investigation, particularly to explore how repeated tDCS sessions interact with antipsychotic treatments and whether they engage adaptive neurobiological mechanisms to reduce symptoms.

We also reported a significant decrease in CBF measured by ASL, an indirect marker of brain activity, in the bilateral superior parietal gyrus, particularly in the precuneus, after frontotemporal tDCS. This is in line with previous findings showing a similar decrease in perfusion in the precuneus after tDCS when using a montage with the anode over the left DLPFC and the cathode over the right supraorbital region, compared to baseline and during stimulation [61]. The precuneus is a key region of the superior parietal gyrus implicated in self-referential mental activity, conscious processing, episodic memory and visuospatial processing [62]. This region shows increased activity at rest compared to during cognitive tasks and serves as a critical node of the default mode network (DMN) [63,64]. This DMN is anti-correlated with attention task-positive networks, such as the frontoparietal network and the cingular-opercular/salience network. Therefore, a potential explanation for the observed decrease in CBF in the precuneus following tDCS is that tDCS disrupted DMN integrity, promoting the activation of these anti-correlated networks and facilitating a reallocation of neural resources to support cognitive demands [65]. This supports the hypothesis that tDCS can shift the brain from an internally-oriented state to an externally-directed state [20,66]. These findings may hold relevance for schizophrenia, where DMN alterations were frequently reported [67–69]. For example, patients with schizophrenia show reduced suppression of the DMN during cognitive tasks, compared to healthy controls (e.g. [70–72]). Furthermore, the DMN is hypothesized to play a role in self-monitoring and in the generation of auditory verbal hallucinations [73,74]. Importantly, repeated sessions of frontotemporal tDCS have been shown to modulate the resting-state functional connectivity between the precuneus and the left TPJ, along with a reduction of auditory hallucinations in patients with schizophrenia [12]. Therefore, the modulation of precuneus activity via tDCS may reflect broader effects on brain network dynamics, offering a potential neurophysiological mechanism underlying the clinical effects of frontotemporal tDCS in schizophrenia, particularly in reducing auditory hallucinations.

Several limitations should be acknowledged. First, an important consideration is the potential role of dopamine in placebo responsiveness [75], although the placebo-controlled design used here partially addresses this. Second, although comparable to previous studies combining noninvasive brain stimulation and PET, our study involved a

relatively small sample size (15 active vs. 15 sham), which may limit the statistical power and generalizability of the findings. Additionally, the study population was limited to young, healthy individuals, which may limit the applicability of the results to a broader population. Further research is necessary to determine whether the observed effects can be translated to individuals with dopamine dysregulation or altered brain connectivity in the frontotemporal network, such as patients with schizophrenia. Furthermore, while the study focused on neuroimaging data, incorporating behavioral assessments would help provide a more comprehensive understanding of the neural mechanisms underlying tDCS modulation. Finally, it is possible that some mechanisms responsible for the therapeutical effects of frontotemporal tDCS require multiple tDCS sessions to develop. This could explain why we did not observe significant changes in white matter microstructural integrity following a single session of active tDCS compared to sham, as such changes has been reported after repeated sessions in older adults [21] or patients with mild cognitive impairment [22]. Future studies should explore the effects of repeated tDCS sessions to further elucidate therapeutic mechanisms.

To conclude, the present study provides the first evidence that frontotemporal tDCS induces dopamine release in polysynaptically connected subcortical regions, particularly the left executive striatum, and modulates cerebral blood flow in the precuneus. This study, conducted with a single session of tDCS in healthy individuals, provides valuable insights into the neurophysiological mechanisms of tDCS, particularly when applied using a frontotemporal montage, as commonly used in schizophrenia treatment.

## CRediT authorship contribution statement

**Clara Fonteneau:** Writing – original draft, Investigation, Formal analysis, Data curation. **Inés Merida:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Jérome Redoute:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Frédéric Haesebaert:** Writing – review & editing, Investigation. **Sophie Lancelot:** Writing – review & editing, Methodology, Investigation. **Nicolas Costes:** Writing – review & editing, Methodology, Investigation. **Marine Mondino:** Writing – original draft, Supervision, Formal analysis, Data curation. **Jerome Brunelin:** Writing – original draft, Supervision, Resources, Methodology, Conceptualization.

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## Declaration of competing interest

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

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2025.05.006.

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