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ORIGINAL PAPER

Advancing clinical response characterization to frontotemporal transcranial direct current stimulation with electric field distribution in patients with schizophrenia and auditory hallucinations: a pilot study

Marine Mondino[1,2,3] · Clara Fonteneau[1,2,3] · Louis Simon[1,2,3] · Clément Dondé[1,2,3] · Frédéric Haesebaert[1,2,3] · Emmanuel Poulet[1,2,3,4] · Jerome Brunelin[1,2,3]

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Abstract

Transcranial direct current stimulation (tDCS) has been proposed as a therapeutic option for treatment-resistant auditory verbal hallucinations (AVH) in schizophrenia. In such cases, repeated sessions of tDCS are delivered with the anode over the left prefrontal cortex and the cathode over the left temporoparietal junction. Despite promising findings, the clinical response to tDCS is highly heterogeneous among patients. Here, we explored baseline differences between responders and nonresponders to frontotemporal tDCS using electric field modeling. We hypothesized that responders would display different tDCS-induced electric field strength in the brain areas involved in AVH compared to nonresponders.

Using baseline structural MRI scans of 17 patients with schizophrenia and daily AVH who received 10 sessions of active frontotemporal tDCS, we constructed individual realistic whole brain models estimating electric field strength. Electric field maps were compared between responders ($n=6$) and nonresponders to tDCS ($n=11$) using an independent two-sample t test. Clinical response was defined as at least a 50% decrease of AVH 1 month after the last tDCS session.

Results from the electric field map comparison showed that responders to tDCS displayed higher electric field strength in the left transverse temporal gyrus at baseline compared to nonresponders ($T=2.37$; $p=0.016$; 32 voxels).

These preliminary findings suggested that the strength of the tDCS-induced electric field reaching the left transverse temporal gyrus could play an important role in the response to frontotemporal tDCS. In addition, this work suggests the interest of using electric field modeling to individualize tDCS and increase response rate.

Keywords tDCS · Electric field · Modeling · Auditory hallucinations · Schizophrenia

Introduction

Auditory verbal hallucinations (AVH) are usually defined as the experience of hearing voices in the absence of external stimuli. AVH are one of the core symptoms of schizophrenia with a lifetime prevalence of 64–80% of patients with schizophrenia [1]. The presence of AVH is associated with poorer real-word functioning [2]. AVH are usually treated with antipsychotic medication. However, up to 30% of patients using antipsychotic medications still experience AVH [3]. In such cases, transcranial direct current stimulation (tDCS) has been proposed as an add-on treatment (for a review, see [4]). tDCS is a noninvasive brain stimulation technique which consists in applying a weak direct electrical current through two electrodes placed on the scalp. Through

✉ Jerome Brunelin
jerome.brunelin@ch-le-vinatier.fr

1 INSERM, U1028; CNRS, UMR5292; Lyon Neuroscience Research Center; PSYR2 Team, 95 bd pinel, F-69000 Lyon, France

2 Lyon University, Université Lyon 1, UCBL, 69000 Villeurbanne, France

3 Centre Hospitalier Le Vinatier, Bron, France

4 Emergency Psychiatry Unit, Edouard Herriot Hospital, Lyon University Hospital, Lyon, France

the induction electric fields within the brain, tDCS modulates cortical excitability and can, in turn, induce behavioral and clinical changes. Most of the studies investigating the therapeutic effect of tDCS on AVH have used a ten-session regimen of frontotemporal tDCS with the anode placed over the left prefrontal cortex and the cathode placed over the left temporoparietal junction (*e.g.* [5],). This frontotemporal tDCS montage was proposed based on neuroimaging studies and cognitive models of AVH in patients with schizophrenia, which have highlighted structural and functional abnormalities in frontotemporal areas involved in speech generation and speech perception [6–8].

Several randomized sham-controlled studies have reported promising beneficial effects of frontotemporal tDCS on AVH in patients with schizophrenia [5, 9–11], but some other failed to demonstrate the superiority of active tDCS over sham to alleviate AVH [12, 13]. Numerous factors may explain the observed discrepancies among studies such as methodological differences (e.g. electrode montage, number of sessions) and clinical differences between samples of patients (e.g. level of treatment-resistance, sample of patients with schizoaffective disorder and/or schizophrenia) (for a review of methodological, clinical and demographic differences between studies, see [4]). In addition, the brain state at the time of the stimulation may influence clinical outcomes [14]. These discrepancies claim for a better understanding of tDCS mechanisms on the brain and for the need of optimizing brain stimulation treatment, such as the accurate identification of potential responders and nonresponders for these brain stimulation treatments [15].

Some studies have suggested that the variability in response to tDCS may be related to differences in the electric fields induced in the brain. For instance, Laakso et al. have modeled the tDCS-induced electric fields in each individual subject based on their structural MRI and have investigated the relationship between these estimated electric fields and the effect of tDCS on motor cortical excitability. They reported that the individual effects of tDCS on motor cortical excitability were related to individual differences in the electric fields in the motor cortex [16]. In a retrospective exploratory study, we aim to investigate whole-brain differences in electrical field distribution between responders and nonresponders to frontotemporal tDCS in a sample of patients with schizophrenia presenting with daily refractory AVH. We used a modeling approach to estimate the electrical field distribution based on the patients' structural MRI acquired at baseline. We hypothesized that responders to frontotemporal tDCS will display differences in electric field strength in brain areas involved in AVH in comparison with nonresponders.

Materials and methods

Participants

The current study included 17 patients with schizophrenia who had received active frontotemporal tDCS in a randomized sham-controlled study between February 2009 and April 2016, and who had undergone a structural T1-weighted MRI acquisition (data from 11 patients were previously published in [17]). Patients met DSM-IV-TR criteria for schizophrenia and presented with refractory auditory hallucinations defined as the persistence of daily AVH without remission despite antipsychotic medication at an adequate dosage for at least 3 months. Exclusion criteria included significant neurological illness, head trauma, history of a seizure not induced by drug withdrawal, current alcohol or drug abuse, or inability to provide informed consent. Medication was kept unchanged throughout the study period (from the beginning to the end of the follow-up period, one month after tDCS—D28).

The study was approved by a local ethics committee (Comité de Protection des Personnes Sud-Est VI, France, AU711, on 2008/12/01), authorized by the French authorities (AFSSAPS, registration number 2008-A01226-49) and conformed to international standards for testing with human participants (Declaration of Helsinki). All patients provided written informed consent prior to the start of the experiment. The study was registered in the clinicaltrials.gov database (registration number: NCT00870909).

tDCS procedure

tDCS was delivered using a NeuroConn device (Ilmeneau, GmbH) with two 35-cm^2 saline-soaked sponge electrodes placed over the scalp of participants. The anode was placed over the left prefrontal cortex (with the center of the electrode placed midway between F3 and FP1 according to 10/20 EEG electrode placement system) and the cathode was placed over the left temporoparietal junction (with the center of the electrode placed midway between T3 and P3). Electrode montage (position and angle-orientation, as depicted in Fig. 1) was kept consistent across repeated sessions and participants. The intensity was set at 2-mA, ramp up/down 30-s for a 20-min duration. tDCS sessions were delivered twice a day on 5 consecutive working days (10 sessions). The two daily sessions were separated by at least 3 h. Details about tDCS parameters and procedure have been previously published in [5, 17].

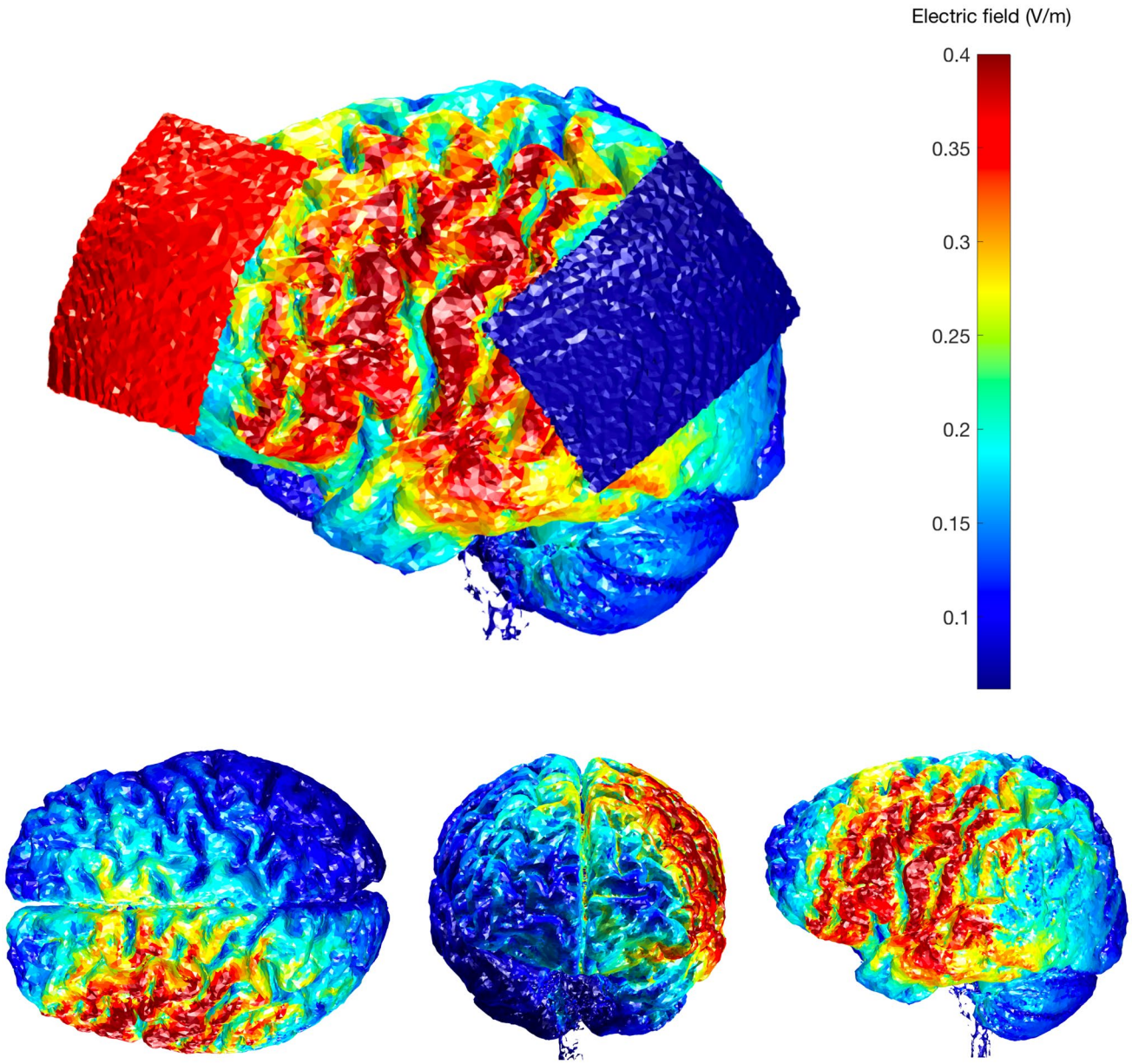

Fig. 1 Estimation results of the tDCS-induced electric field distribution of the frontotemporal montage with two 7×5 cm electrodes and a current intensity of 2 mA. The anode was placed over the left prefrontal cortex (midway between Fp1 and F3), and the cathode was placed over the left temporoparietal junction (midway between T3 and P3). The electric field strength was scaled from 0 (minimum: blue) to 0.4 V/m (maximum: red). Electric field simulation was performed with the "Realistic vOlumetric-Approach to Simulate Transcranial Electric Stimulation" toolbox (ROAST, v2.7.1; [23]) based on individual structural MRI

Clinical ratings

Global severity of AVH was assessed by trained psychiatrists with the Hallucination Change Scale (HCS; [18–20]). Before tDCS regimen (D0), each participant was required to generate a detailed description of their AVHs over the previous 24 h, which was defined as the "baseline severity" and was scored as a 10. The HCS was then scored on subsequent assessments (after the 5 days of tDCS—D5, and one month after tDCS—D28) by requesting the patient to generate a new narrative description of AVH over the previous 24 h, which was compared to the baseline description. Subsequent HCS scores were thus ranged from 0, corresponding to no hallucinations, to a maximum score of 20, corresponding to hallucinations twice as severe as baseline (10 means no changes in AVH). Raters and patients were blind to the tDCS condition.

Severity of general symptoms of schizophrenia was assessed at baseline with the Positive and Negative Syndrome Scale (PANSS; [21]). Secondary descriptive measures of specific characteristics of AVH at baseline was also assessed by the French version [22] of the seven-item Auditory Hallucination Rating Scale (AHRS; [18]). This scale evaluates frequency, realness, perceived loudness, length of hallucination instances, attentional salience (the degree to which hallucinations capture attention and alter on-going thought and behavior), induced distress, and the number of distinct speaking voices.

Clinical response to tDCS

According to Hoffman et al.'s definition (2003) [18], tDCS responders were defined as patients who presented with an at least 50% reduction of their AVH, as indicated by an HCS ≤ 5. HCS was rated at D0, D5 and D28. Response was assessed at 1 month after tDCS (D28).

Electrical field modeling

To assess electrical field distribution differences between responders and nonresponders, we evaluated all available baseline structural T1-weighted MRI scans of patients who received active tDCS ($n = 17$). MRI scans were acquired using a 1.5 T Magnetom scanner (Siemens) at D0 before the stimulation sessions. A 3-dimensional (3D) anatomic T1-weighted sequence covering the whole brain volume was used with the following parameters: 176 transverse slices; TR = 1970 ms; TE = 3.93 ms; field of view = 256 mm^2; voxel size = 1 mm^3.

Electric field strength was modeled for each subject with the "Realistic vOlumetric-Approach to Simulate Transcranial Electric Stimulation" toolbox (ROAST, v2.7.1; [23]) based on individual structural MRI coupled with electrode sizes, positions and orientations, and current intensity (see Fig. 1 for an example of an individual electric field strength map). It is important to note that this method allows an estimation of the electric field induced by tDCS, but is not a measured value. Resulting electric field strength maps for each participant were normalized into MNI space by calculating deformation fields based on each T1-weighted anatomical sequence using an MNI template. Electric field maps were then spatially smoothed using a 3-mm^3 full-width half-maximum (FWHM) Gaussian kernel. Normalization and smoothing were done using SPM12 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging). Whole-brain differences in electric field strength across space between responders and nonresponders were examined using an independent two-sample t test conducted in SPM12 toolbox. A p-value of $p_{unc} = 0.05$ and a threshold cluster size of $k > 20$ voxels was used to determine significance. The anatomical location of cluster peaks was determined on the basis of the neuromorphometrics atlas in SPM (Neuromorphometrics, Inc. https://neuromorphometrics.com/).

Clinical data analyses

Statistical comparisons of socio-demographic and clinical data between responders and nonresponders were performed using two-tailed Student's t tests for quantitative variables and Fischer's exact tests for qualitative variables. Socio-demographic and clinical data included patients' age, handedness, sex, years of education, illness duration, clinical symptoms of schizophrenia at baseline assessed by the PANSS and AVH severity at baseline assessed by the AHRS. The significance level was set at $p < 0.05$ for all analyses.

Results

Clinical response

Out of the 17 patients with schizophrenia and AVH that were included in the analyses, 6 were considered as responders to tDCS and 11 as nonresponders. The responders and nonresponders did not show a significant difference in age, handedness, sex, years of education, illness duration, PANSS total scores and AHRS scores at baseline (see Table 1). In the tDCS responder group, mean HCS was 4.4 (standard deviation = 3.6) at D5 which corresponds to a 56% decrease in AVH and 3.1 (1.8) at M1, which corresponds to a 69% decrease in AVH. In the tDCS nonresponder group, mean HCS was 8.7 (1.3) at D5, which corresponds to 13% decrease in AVH and 9.3 (3.6) at D28, which corresponds

Table 1 Patients' socio-demographic and clinical characteristics

	tDCS responders ($N = 6$)	tDCS nonresponders ($N = 11$)	p-value
Sex (female / male)	4 / 2	3 / 8	0.16
Handedness (right /left)	5 / 1	10 / 1	1
Age (years)	36.3 (9.9)	34.9 (8.7)	0.76
Education (years)	11.8 (3.5)	11.3 (2.9)	0.73
Illness duration (years)	9.3 (7.4)	12.5 (9.4)	0.49
PANSS score	68.7 (14.8)	69.5 (14.1)	0.91
AHRS score	28.3 (2.4)	26.8 (4.9)	0.50

Characteristics are expressed as mean (standard deviation). Quantitative and qualitative variables were compared using two-tailed Student's t tests and Fischer's exact tests, respectively. No significant differences were found between tDCS responders and nonresponders

Table 2 Individual data of antipsychotics treatments and hallucinations change score (HCS) in responders and nonresponders after the 5 days of tDCS (D5) and 1 month after (D28)

#	tDCS response	Antipsychotics treatments: molecule (dose)	HCS at D5	HCS at M1
1	Nonresp	Risperidone (9 mg/d)	10	12
2	Nonresp	Haloperidol (30 mg/d), Olanzapine (30 mg/d), Cyamemazine (50 mg/d)	6	6
3	Nonresp	Olanzapine (30 mg/d), Levomepromazine (20 mg/d)	10	6
4	Nonresp	Clozapine (400 mg/d)	8	6
5	Nonresp	Cyamemazine (25 mg/d), Haloperidol LP (4 * 50 mg/month)	10	10
6	Nonresp	Quetiapine (800 mg/d)	8	10
7	Nonresp	Clozapine (400 mg/d)	8	6
8	Nonresp	Olanzapine (10 mg/d)	8	6
9	Nonresp	Quetiapine (800 mg/d)	10	10
10	Nonresp	Loxapine (75 mg/d), Risperidone LP (50 mg/14d)	10	16
11	Nonresp	Olanzapine (40 mg/d), Abilify (10 mg/d)	8	14
12	Resp	Quetiapine (500 mg/d)	0	0
13	Resp	Haloperidol (6 mg/d)	7.5	3.5
14	Resp	Clozapine (400 mg/d), Aripiprazole (15 mg/d)	5	5
15	Resp	Clozapine (300 mg/d)	6	2
16	Resp	Risperidone (8 mg/d)	0	4
17	Resp	Olanzapine (15 mg/d)	8	4

HCS hallucination change score (range from 0, corresponding to no hallucinations, to a maximum score of 20, corresponding to hallucinations twice as severe as baseline (10 means no changes in hallucinations), *D5* after the 5 days of tDCS, *D28* one month after tDCS, nonresp: nonresponders; resp: responders

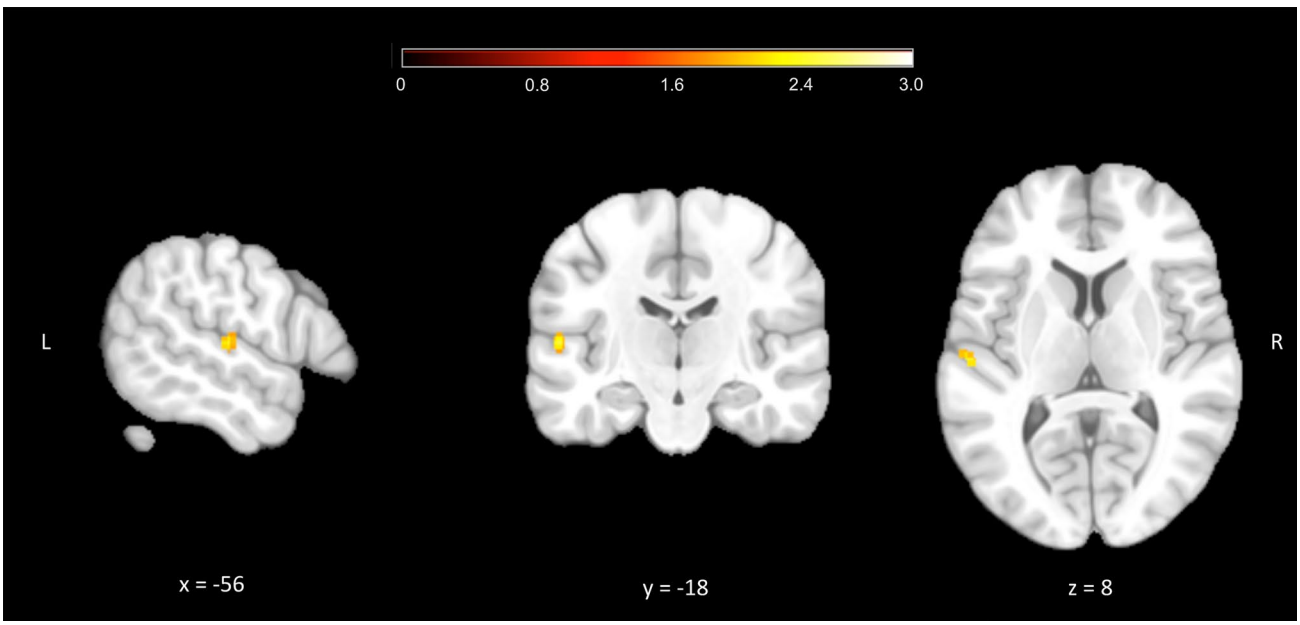

Fig. 2 Whole-brain differences in electric field strength between responders and nonresponders to frontotemporal tDCS. Significant cluster of increased electric field strength in responders compared to nonresponders (responders > nonresponders contrast). Clusters were considered as significant when falling below an uncorrected $p < 0.05$ and $k > 20$. Results are superimposed on axial, coronal and sagittal slices from an MNI template

to a 7% decrease in AVH. Individual data are provided in Table 2. Between group HCS differences were statistically significant at D5 ($p=0.002$) and D28 ($p=0.001$).

Comparison of electric field strength between responders and nonresponders

Whole-brain comparison of electric field strength maps showed that responders had significantly higher electric field strength in a cluster in the left transverse temporal gyrus, within the superior temporal gyrus, compared with nonresponders (Brodmann area 41, i.e. primary auditory cortex, MNI cluster peak coordinates: x,y,z = −56, −18, 8; $T=2.37$; $p=0.016$; 32 voxels; Fig. 2). The reverse contrast (responders < nonresponders) showed no significant results.

Discussion

In this exploratory study, we investigated whether the estimated tDCS-induced electric field can explain the clinical response in patients with AVH and schizophrenia. We reported that patients who responded to tDCS, with at least a 50% reduction of their AVH within the month following the ten sessions of frontotemporal tDCS, displayed higher modeled electric field strength in a brain area within the left transverse temporal gyrus, compared with patients who did not respond to tDCS.

Our results support the hypothesis that the electric field distribution is likely an important explanatory factor regarding the clinical effects evoked by tDCS. These results are in line with studies that have established a link between individual tDCS-induced electric fields and some tDCS-induced effects such as the effects on motor cortical excitability [16]. In a magnetic resonance spectroscopy study, Antonenko et al. investigated the effects of tDCS on brain metabolites, specifically GABA and glutamate concentrations. They reported that the tDCS-induced modulation of GABA concentrations within the targeted brain area was significantly associated with the tDCS-induced electric field strengths in this brain area [24]. The observed differences in electric field distribution may be related to anatomical differences such as the gyri/sulci morphology, more precisely the sulcal depth, as well as the thicknesses of the skull and the CSF layer between the skull and the cortex [25, 26]. Further studies are needed to better characterize the influence of these variables on tDCS effects.

Specifically, responders differ from nonresponders to tDCS with regards to the extent of its effect on the left transverse temporal gyrus. This region, also called Heschl's gyrus, corresponds to the primary auditory cortex. Numerous structural and functional studies have highlighted the implication of the primary auditory cortex in AVH ([27], see also [28] for a review). For instance, at the structural level, gray matter volume reductions in the left Heschl's gyrus were significantly associated with the severity of AVH [29]. In addition, reduced cortical thickness in the left Heschl's gyrus was reported in schizophrenia patients with AVH compared to patients without AVH [30]. A metaanalysis of neuroimaging studies reported the activation of the left primary auditory cortex during the experience of AVH in patients with schizophrenia [31]. They also reported a decreased activation of the same area during the processing of external auditory stimuli. The contribution of the primary auditory cortex to AVH pathophysiology may explain why higher electric field strength reaching this area is associated to a better clinical response to tDCS. In parallel, it was recently reported that subgroups of schizophrenia patients with intact early auditory processing (EAP) show significant reduction of AVH after tDCS in comparison to subgroups with EAP impairments [11]. Given evidence that EAP impairment is associated with reduced connectivity within the primary auditory cortex [32], it is likely that effective tDCS-based modulation of local connectivity of this cortical area is critical for AVH reduction.

Although the left frontotemporal montage seems to be the consensus in the tDCS literature for AVH [4], the choice of this montage has to be confronted with other options. Indeed, it might be relevant to target other brain areas or brain networks involved in AVH, such as the salience network [33], or to individualize the targeting, for instance based on the fMRI capture of AVH [34].

Due to its exploratory nature, our study has several limitations that should be acknowledged. First, our findings should be taken with caution since the small sample size may limit generalizability of results. Further studies with a larger sample and a more stringent statistical threshold are needed to confirm these preliminary findings. Moreover, two left-handers were included in the study and we cannot exclude that handedness could have an influence on electric field distribution and on AVH. Larger sample size studies could help examining the effect of handedness on tDCS-induced electric field estimation. Second, the electric field modeling was conducted at the individual level using the electrode position as defined by the tDCS protocol, based on the 10–20 system of electrode placement. However, the study design did not allow us to check the exact electrode position on the MRI acquisition. In addition, we cannot exclude that the position of the electrodes may have slightly differed among the 10 sessions of tDCS for each subject. Third, it is important to acknowledge that the model used here only reflects the theoretical electric field distribution induced by a given tDCS montage (electrode positioning and current intensity) and not the tDCS-induced effects on brain activity, which are also likely related to the session duration and the

number of repeated sessions. Fourth, since there is no consensual definition of clinical response for AVH, we defined the clinical response to tDCS as a reduction of the AVH of at least 50% as measured by the HCS. Despite using a 50% cut-off may have several limitations [35], this outcome was chosen based on the literature on the effect of repetitive transcranial magnetic stimulation on AVH [18–20]. Moreover, the HCS has the advantage of providing an indication of the general severity of AVH and, therefore, may be suitable for studying AVH evolution over the course of the study, regardless of the phenomenological heterogeneity of AVH among patients. Fifthly, the electric field distribution may not be the only factor that has influenced the clinical response to tDCS. While we compared responders and nonresponders for several sociodemographic and clinical characteristics, other factors that have been shown to influence the clinical response to tDCS were not measured, such as the smoking status [36], the cognitive profile [11], and the catechol-O-methyltransferase gene polymorphism (rs4680) [37]. Finally, our analyses were done a posteriori at the group level and cannot be used to predict the clinical response at the individual level. Further studies involving larger samples are needed to identify specific predictors of response to tDCS.

To conclude, our exploratory study suggests a link between the clinical response to frontotemporal tDCS in patients with AVH and the amount of tDCS-induced electric field in the left primary auditory cortex. In addition, our study supports the interest of modeling the electric field distribution to increase the response rate to tDCS. Future studies should explore whether the use of electric field modeling could help finding the best individual tDCS parameters (electrode position and orientation) to produce the highest electric field strength in the left primary auditory cortex and could translate into a better clinical response to tDCS.

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