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Brain-wide activation involved in 15 mA transcranial alternating current stimulation in patients with first-episode major depressive disorder

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ABSTRACT

Background Although 15 mA transcranial alternating current stimulation (tACS) has a therapeutic effect on depression, the activations of brain structures in humans accounting for this tACS configuration remain largely unknown.

Aims To investigate which intracranial brain structures are engaged in the tACS at 77.5 Hz and 15 mA, delivered via the forehead and the mastoid electrodes in the human brain.

Methods Actual human head models were built using the magnetic resonance imagings of eight outpatient volunteers with drug-naïve, first-episode major depressive disorder and then used to perform the electric field distributions with SimNIBS software.

Results The electric field distributions of the sagittal, coronal and axial planes showed that the bilateral frontal lobes, bilateral temporal lobes, hippocampus, cingulate, hypothalamus, thalamus, amygdala, cerebellum and brainstem were visibly stimulated by the 15 mA tACS procedure.

Conclusions Brain-wide activation, including the cortex, subcortical structures, cerebellum and brainstem, is involved in the 15 mA tACS intervention for first-episode major depressive disorder. Our results indicate that the simultaneous involvement of multiple brain regions is a possible mechanism for its effectiveness in reducing depressive symptoms.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ 15 mA transcranial alternating current stimulation (tACS) at a frequency of 77.5 Hz delivered via a montage of the forehead and both mastoids is a safe and effective intervention for chronic insomnia and depression over 8 weeks and can non-invasively send electrical currents to deep brain areas where stereoelectroencephalography (SEEG) electrodes were implanted in awake adult patients with drug-resistant epilepsy. However, we still do not know whether other brain regions without SEEG implantation are involved in this 15 mA tACS treatment configuration in awake humans.

WHAT THIS STUDY ADDS

⇒ We first revealed that the cerebellum, brainstem, cortex and subcortical structures are involved in 15 mA tACS at 77.5 Hz intervention for first-episode major depressive disorder.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results provide direction for future studies to explore why the 15 mA tACS procedure appears to be mechanistically linked to multiple brain structures, especially the cerebellum and brainstem, in subjects with depression or other brain disorders. The simultaneous brain-wide activation induced by 15 mA tACS may be one of the mechanisms underlying this stimulation for depression.

INTRODUCTION

Transcranial electrical stimulation (tES) is one of the non-invasive brain stimulation techniques showing promising results in modulating treatment outcomes in several psychiatric and neurological disorders.[1] It has attracted increasing attention in neuroscience.[2] Traditionally, applying weak direct (transcranial direct current stimulation, tDCS) or alternating (transcranial alternating current stimulation, tACS) currents with tES is particularly interesting as it provides safe and tolerable stimulation at low cost and high portability. These features make tES approaches promising for a wide range of clinical applications. However, the classical tES methods have received substantial criticism, arguing that stimulation effects were weak, highly variable or could not be replicated. Some authors even questioned whether current intensities in the 1–2 mA range commonly used for tES cause sufficient electric field strength inside the brain to elicit effects.

tDCS, as one form of tES, is thought to present its effect by changing neuronal excitability via tonic alterations of the neuron's

resting membrane polarisation, and the rhythmic shifts in the membrane potentials during tACS are believed to result in neuronal entrainment.[2 3] The stimulation of tDCS can reach deep brain areas simultaneously with computational analysis approaches.[3 4] Meanwhile, 1 mA alpha tACS stimulation can also cause a more prominent power increase in the alpha-band frequency, as revealed by a magnetoencephalogram.[2] However, there is a lack of regional information on the electric field.[2] Furthermore, the efficiency of the tACS with a sizeable current intensity, such as 15 mA, is still unknown for the clinical treatment of patients with depression and insomnia.[5–7]

For human studies, different studies have applied different current intensities to treat insomnia, chronic painful conditions, anxiety and depression.[5 6 8–10] Our recent studies have demonstrated that tACS with a current of 15 mA and a frequency of 77.5 Hz delivered via a configuration of the forehead and both mastoids was a safe and effective intervention for chronic insomnia and depression over 8 weeks.[5 6] However, other studies that applied tACS currents less than 4 mA for depression and insomnia showed inconsistent results.[8 9 11] Therefore, discovering the locations where different tACS currents stimulate the various brain regions is urgently needed. Stimulating electrical currents less than 4 mA tend to reach superficial areas locally, such as the cerebral cortex.[8 11] However, no studies have reported on the whole picture to identify which intracranial areas are induced by the sizeable alternating current of 15 mA of tACS, although this amount of electric stimulation can definitely and precisely arrive at the intracranial areas such as the hippocampus, insula and amygdala in awake humans.[10]

Recently, we first used stereoelectroencephalography (SEEG) electrodes in awake patients with drug-resistant epilepsy to observe whether there were any changes in local field potentials (LFPs) in the hippocampus, insula and amygdala during tACS at different currents. Our results found that the hippocampus, insula and amygdala can directly record the LFP changes with the increase in extracranial non-invasive alternating current during the 15 mA tACS procedure that we used,[10] suggesting that the 15 mA tACS protocol can directly penetrate the skin, skull and brain tissue to arrive at deeper brain regions. However, we still need to determine whether this treatment configuration can stimulate other brain regions that have yet to be implanted with SEEG electrodes, especially those closely related to life centres and movements, such as the brainstem and cerebellum.[12 13] It is currently impossible to implant SEEG electrodes directly into the brainstem and cerebellum to study whether the magnitude of extracranial currents can affect those above-mentioned unique brain regions in awake humans.

Luckily, simulations have been used to mimic the process of brain activity to better model the anatomical and functional variations in the human brain.[14] For example, specific simulations have been adopted to understand which brain areas are the main stimulated targets and the relationship between stimulation parameters and clinical responses, such as those reported in deep brain stimulation and Gilles de la Tourette syndrome.[14] Therefore, the simulation analysis is suitable for exploring the variations of LFPs induced by 15 mA tACS in the brain, including the brain areas implanted with SEEG electrodes, the brainstem and the cerebellum.

Unlike previously reported results,[15] we have found that the 15 mA tACS procedure, in which the electrical stimulation travels via the forehead and mastoid electrodes, had a therapeutic effect in patients with chronic insomnia and those with drug-naïve, first-episode major depressive disorder (MDD).[5 6] Adhering to this study's tACS protocol, we used a realistic finite element modelling method to explore the electric field distributions induced by 15 mA tACS in the human brain to improve our understanding of brain structures, especially the brainstem and the cerebellum—challenging areas in which to obtain corresponding results by SEEG in awake humans.

METHODS

Study design

This simulation study was conducted in Chinese patients with first-episode naïve MDD. All participants received 20 sessions of tACS at 77.5 Hz and 15 mA over 4 weeks, with once-daily sessions every weekday. On the day following the last tACS intervention, the enrolled participants completed magnetic resonance imaging (MRI) scans that were applied to simulation analysis by the SimNIBS software.

Participants

Patients with depressive disorders from the outpatient clinic service of Xuanwu Hospital of Capital Medical University, Beijing, China, were recruited for enrolment in the study between August 2020 and December 2021.

The inclusion criteria were: (1) 18–60 years old, Han Chinese; (2) a diagnosis of unipolar, non-psychotic MDD based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision[5]; (3) a 17-item Hamilton Depression Rating Scale (HDRS-17) total score higher than 17 points at baseline; (4) an acute episode of the illness; and (5) no previous psychoactive drug treatment.

The exclusion criteria were: (1) a current or lifetime history of comorbid Axis I psychiatric disorders (including panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, anorexia nervosa, bulimia nervosa, generalised anxiety disorder) or antisocial personality disorder in Axis II as assessed via the Mini-International Neuropsychiatric Interview, Chinese version 5.0[5]; (2) a current or lifetime bipolar disorder; (3) a current or lifetime psychotic disorder; (4) a current or history of organic brain disorders or neurological disorders; (5) acute suicidal risk as shown by a score of 3 or 4 on the suicide item of HDRS-17; (6) previous or current exposure to electroconvulsive therapy (ECT), modified ECT, transcranial magnetic

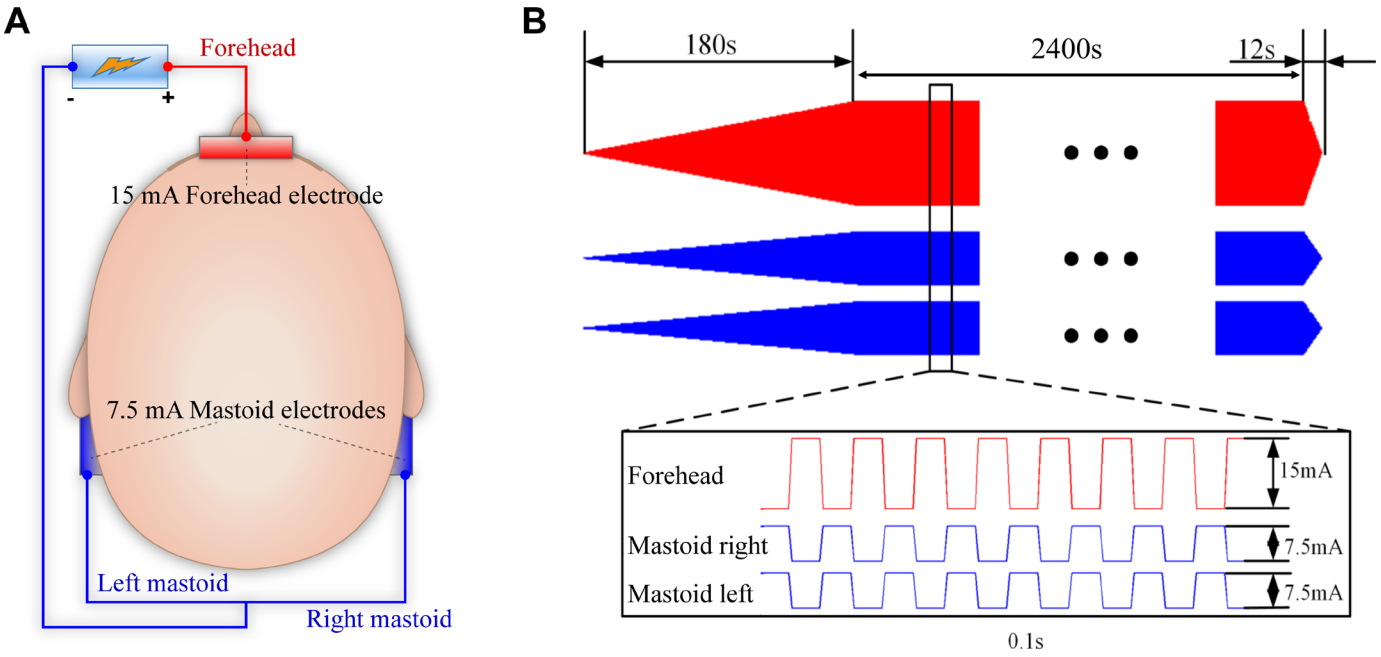

Figure 1 Schematic view of the transcranial alternating current stimulation (tACS) protocol. (A) Stimulation configuration. Three electrodes were used: one was connected to the electrode over the forehead (15 mA, Fp1, Fpz, Fp2) and two were connected to the electrodes over the left and right mastoids (7.5 mA for each side). At a specific moment, the red electrode was the anode, and the blue return electrodes were the cathode (vice versa). (B) Active stimulation paradigm. Ramp-in and ramp-out were 180 and 12 s, respectively, with 2400 s of active stimulation for 77.5 Hz tACS. The forehead and both mastoid areas were at opposite phase at any given point during stimulation.

stimulation, tDCS, tACS or other neurostimulation treatments; (7) cochlear implant, cardiac pacemaker and implanted device or metal in the brain; (8) previous or current psychotropic treatment; (9) previous or current psychotherapy; (10) pregnant or lactating; (11) participation in a concurrent clinical trial; and (12) refusal to sign the informed consent to participate in the trial.

tACS stimulation

The tACS stimulation procedure was conducted using a similar method that was reported previously.[5 6] Participants reclined comfortably on a hospital bed while receiving alternating current stimulation delivered with a tACS device (Nexalin Technology, Houston, Texas, USA) approved by the Chinese National Medical Products Administration. As previously described, the electrodes were placed at the forehead and the mastoid regions (figure 1A). Based on the international 10/20 system, a 4.45 cm×9.53 cm electrode was placed on the forehead parallel to Fpz, Fp1 and Fp2. Two 3.18 cm×3.81 cm electrodes were fixed on both sides of the mastoid region.

MRI data acquisition

Structural MRI data were acquired on a Siemens 3T TIM Trio scanner (Siemens Healthcare, Erlangen, Germany) equipped with a 12-channel head coil. High-resolution T1-weighted images were obtained with a three-dimensional volumetric T1-weighted magnetisation-prepared rapid acquisition gradient echo sequence (repetition time/echo time (TR/TE)=1600/2.13 ms, T1=1000 ms, flip angle=9°, field-of-view (FOV)=256×224 mm^2, matrix size=256×224, slice thickness=1.0 mm, voxel dimensions=1.0×1.0×1.0 mm^3). Diffusion tensor images (DTI) were acquired using a custom DTI sequence—spin echo-echo planar imaging with the following parameters: 40 axial slices, TR/TE=11 000/98 ms, slice thickness=2 mm; no gap; in-plane resolution=2×2 mm^2; matrix size=128×116; 30 weighted diffusion scans (b=1000 s/mm^2) and 1 unweighted (b=0 s/mm^2) scan.

Modelling the electric field distribution

SimNIBS software (V.3.2, www.simnibs.org) was used to segment the MRI data of patients with first-episode naïve MDD to build a realistic finite element model for performing simulations of the electric field distribution in the brain. The human brain consists of the scalp, skull, cerebrospinal fluid (CSF), grey matter and white matter (WM). The forehead was regarded as the anode with a size of 4.45×9.53 cm^2 (42.41 cm^2), and the bilateral mastoid areas as the cathodes with each size of 3.18×3.81 cm^2 (12.12 cm^2) at a given moment. The conductivity of each layer of the head model was set as follows: σ_{scalp}=0.465 S/m,[16] σ_{skull}=0.010 S/m,[16] σ_{CSF}=1.654 S/m,[16] σ_{GM}=0.275 S/m,[16] σ_{WM}=0.126 S/m,[16] $\sigma_{electrode}$=1.750 S/m.[17] The FMRIB Software Library (FSL) was applied to register the DTI to the T1 image to obtain the anisotropy of WM.

The tACS stimulation waveform was a square wave with an average amplitude of 15 mA distributed equally from the forehead to the mastoid areas (amplitudes are reported as zero-to-peak), 180 s for starting from 0 mA to 15 mA and 12 s for ending from 15 mA to 0 mA

(figure 1B). Our former work found that the average LFPs were significantly linearly correlated with the increasing extracranial currents (all p<0.05) in the hippocampus, insula and amygdala, respectively.[10] Meanwhile, 15 mA was beyond the input upper limit of SimNIBS software. Thus, the forehead electrode was set to 1.5 mA, and the mastoid electrodes on both sides were set to −0.75 mA during the simulation. Therefore, after the simulation results were obtained, they were scaled proportionally.

The electric field was calculated by solving $\vec{E} = -\nabla\varphi$, where $\vec{E}$ was the electric field vector and φ the electric potential. The electric potential φ was computed using an electrostatic formulation with Dirichlet boundary conditions at the electrodes, which were set to fixed potentials.

Data analysis

Data were described as mean (standard deviation (SD)) for continuous variables, performed by SPSS Statistics V.26.0 (SPSS). Cortical areas were divided into the frontal, parietal, temporal and occipital regions using an automated anatomical labelling atlas.[18] All cerebellar subdivisions were combined to generate cerebellum masks. Additionally, pons and medulla masks were built up based on Rosenberg parcellation.[19] Finally, the midbrain template was manually created in MRIcron (https://www.nitrc.org/projects/mricron). We then extracted the averaged value from the mask with each voxel exceeding 1.5 V/m and calculated the spatial overlap percentages of the whole brain and each brain area.

RESULTS

Twenty-four Han Chinese participants with drug-naïve, first-episode MDD were recruited from the outpatient clinic between August 2020 and December 2021, but only eight patients were eligible and agreed to participate in the study due to various reasons (see figure 2). All eight patients were female, with ages ranging from 27 to 60 (mean (SD): 45.3 (13.0) years), and all were right-handed. The demographics and historical correlates of the eight patients are summarised in online supplemental table S1.

Electric field distribution

During the tACS treatments of the patients, higher electric field distributions were observed on the surface of the bilateral frontal lobes, temporal lobes, cerebellum and medulla oblongata, which are physically and spatially close to the stimulating electrode locations (figure 3A). Visualisation of the simulated electric field from the cross-sectional MRI unveiled the global electric field distributions of the brain in five directions (figure 3B–D). In each direction, a cross-sectional MRI was taken every 5 mm, covering the whole brainstem.

Electric field simulations revealed various areas, including the bilateral frontal lobes, cingulate, hippocampus, hypothalamus, thalamus, amygdala, midbrain, pons, medulla oblongata and cerebellum, that were involved in our tACS electrode configurations. In addition, the electric field distributions in the left and right hemispheres of the brain were visibly symmetrical. The sagittal plane showed that the bilateral frontal lobes, cingulate, cerebellum, midbrain, pons and medulla oblongata were visibly significantly changed (figure 3B). In the coronal plane, the higher electric fields were located in the bilateral temporal lobes, hippocampus, hypothalamus, thalamus, midbrain, pons, cerebellum and medulla oblongata (figure 3C). In the axial plane, the bilateral superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, anterior and median cingulate, hippocampus, amygdala, midbrain, pons and the ventral parts of the inferior and superior cerebellum showed higher electric fields (figure 3D). The overall details of the electric field simulations are presented in figure 3.

The values on electric fields of different brain structures and the portions of each cerebral region in the whole-brain voxel and the activated cerebral area in

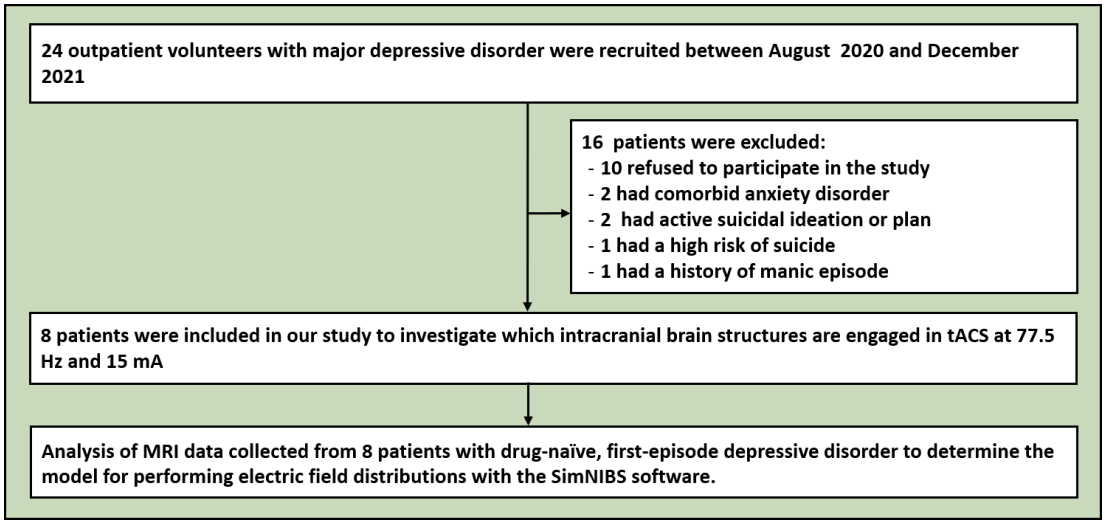

Figure 2 Procedure of the depression diagnosis and clinical treatment in our study. tACS, transcranial alternating current stimulation. MRI, magnetic resonance imaging.

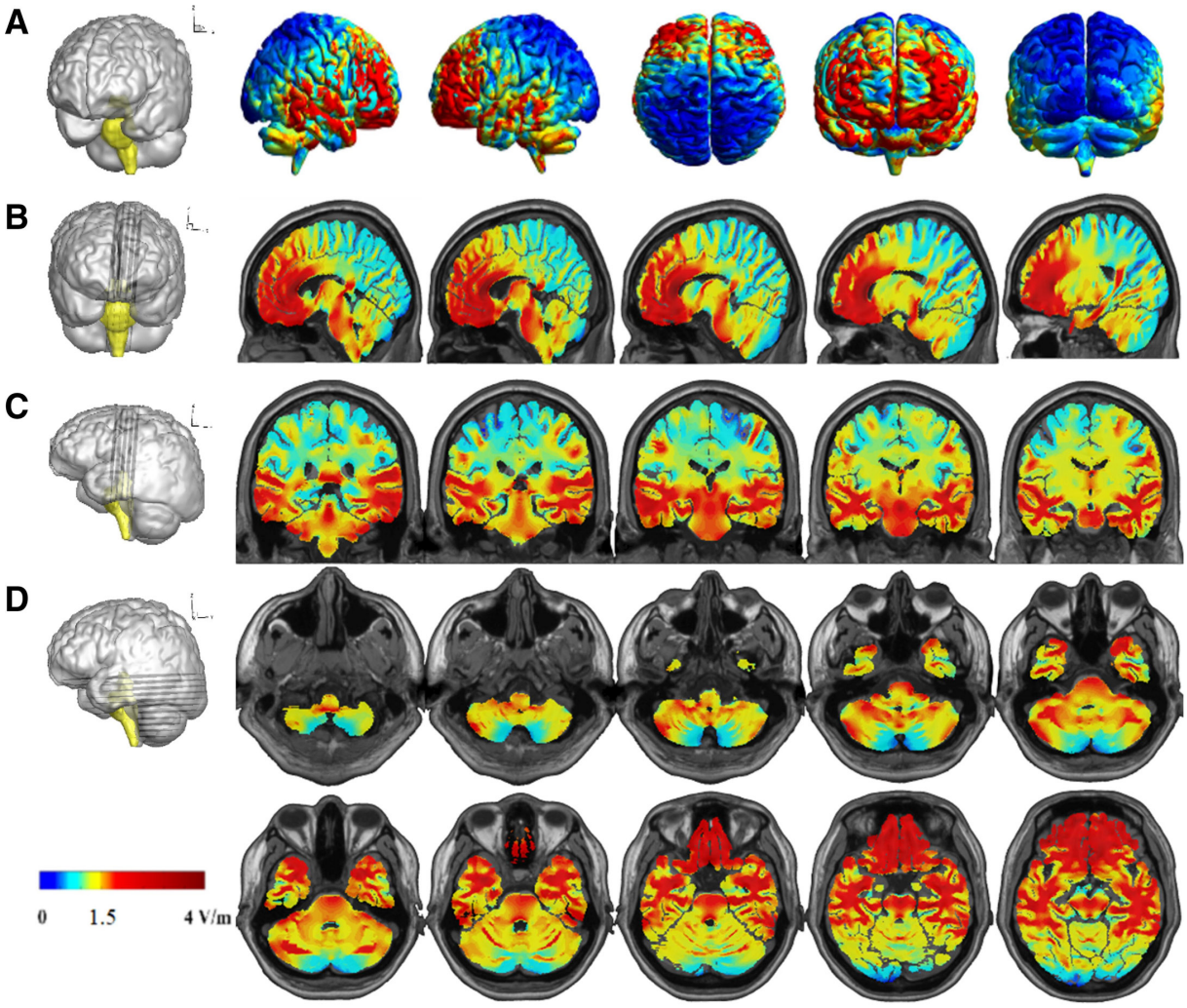

Figure 3 Electric field distributions in the average brain. (A) The electric field distribution on the surface of brain tissue from five angles. (B–D) The electric field distributions were illustrated in different directions, such as the sagittal plane (B), the coronal plane (C) and the axial plane (D), respectively. All sections were through the brainstem. The colour scale was ranged from 0 V/m (blue) to 4 V/m (red).

its own regional voxel with an electric field greater than 1.5 V/m are summarised in table 1. The electric field values for all brain regions were ranged from 1.63 (0.14) to 2.05 (0.41). The highest value of the electric field was in bilateral frontal lobes (2.05 (0.41) V/m), and the lowest electric field value was located in the thalamus (1.63 (0.14) V/m). The biggest percentage level value of the whole-brain voxel with an electric field greater than 1.5 V/m was located in the bilateral frontal lobes (27.19%), followed by bilateral temporal lobes (15.82%), cerebellum (6.34%), cingulate (4.18%) and pons (1.57%). Some areas of the parietal (0.53%) and occipital (0.76%) lobes were also implicated in the tACS procedure. For the proportion of each brain voxel with an electric field greater than 1.5 V/m, their values ranged from 2.60% (bilateral parietal lobes) to 66.23% (midbrain).

The dynamic variation of electric fields in the intracranial brain areas revealed that the brain structures close to CSF have stronger electric fields. The observable prominent variations of intracranial electrical activity included the ventral medulla oblongata, cerebellar tonsils, pontine arm, rostrum and genu of the corpus callosum, the anterior part of the body of the corpus callosum and the splenium of the corpus callosum. One-cycle intracranial change in brain-wide activation induced by the 77.5 Hz, 15 mA tACS, is presented in figure 4 and online supplemental figure S1.

DISCUSSION

Main findings

For the first time, we visibly observed that brain-wide activation was involved during the tACS procedure at 77.5 Hz frequency and 15 mA current via three electrodes on the surface of the forehead and two mastoid electrodes, including the bilateral frontal lobes, bilateral temporal lobes, hippocampus, cingulate, hypothalamus, thalamus, amygdala, cerebellum and brainstem. In addition, we also

Table 1 Electric field values in different visible brain regions stimulated by the transcranial alternating current stimulation

Brain regions	Electric field values (V/m) Mean (SD)	Percentage of whole-brain voxel with an electric field greater than 1.5 V/m (%)	The proportion of each brain voxel with an electric field greater than 1.5 V/m (%)
Bilateral frontal lobes	2.05 (0.41)	27.19	53.49
Bilateral temporal lobes	1.85 (0.26)	15.82	46.56
Cingulate	1.97 (0.40)	4.18	39.69
Bilateral parietal lobes	1.69 (0.19)	0.53	2.60
Cerebellum	1.66 (0.15)	6.34	20.39
Hippocampus	1.83 (0.26)	0.58	24.52
Pons	1.75 (0.21)	1.57	62.23
Midbrain	1.78 (0.20)	0.78	66.23
Bilateral occipital lobes	1.64 (0.14)	0.76	5.69
Medulla oblongata	1.65 (0.19)	0.72	52.15
Amygdala	1.84 (0.26)	0.41	47.72
Hypothalamus	1.70 (0.25)	0.07	14.42
Thalamus	1.63 (0.14)	0.61	21.24

SD, standard deviation; V/m, voltage per metre.

found that the electric field values in the bilateral frontal lobes located below the frontal stimulation electrode were the highest areas, which should be related to the electrode's location. Moreover, the levels of the electric field in the cingulate and the brain areas in the deep parts of the brain close to the CSF tended to have more visibly prominent electrical activities. Most importantly, we first revealed that the cerebellum and brainstem, cortex and subcortical structures are involved in the 15 mA tACS at 77.5 Hz intervention for patients with drug-naïve, first-episode MDD. These findings indicate that concomitantly stimulating these brain structures may be one of the vital basic mechanisms of tACS in treating depression.

Previous human studies on the brain areas/structures involved in patients with depression versus healthy controls showed that several brain areas have roles in the underlying circuit mechanisms of depression.[20–23] Brodmann area 10 and the amygdala were hub structures associated

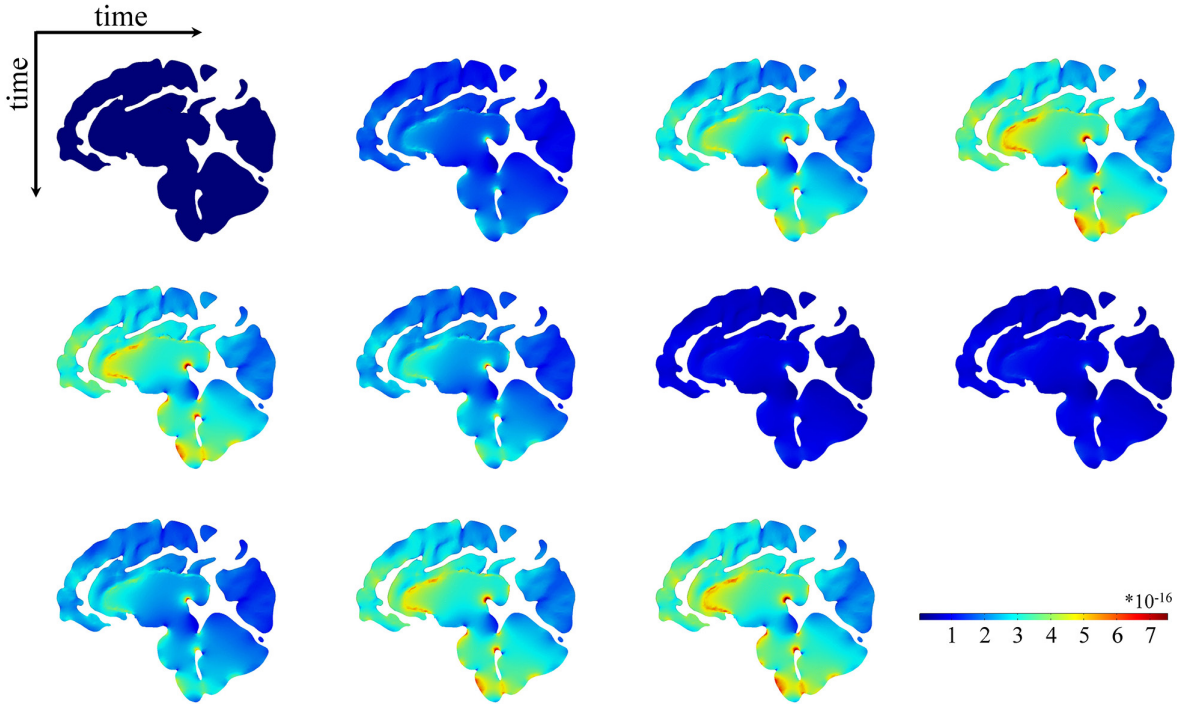

Figure 4 The one-circle intracranial electrical activity (energy density: J/m^3) induced by 77.5 Hz, 15 mA transcranial alternating current stimulation.

with all deep brain stimulation targets for treatment-resistant depression via probabilistic tractography using diffusion MRI data from 100 healthy volunteers drawn from the Human Connectome Project datasets.[20] Furthermore, patients with unmedicated bipolar depression and unmedicated MDD and treatment-resistant depression showed abnormal connectivity in various brain sites, including the cingulum bundle, uncinate fasciculus, medial forebrain bundle, anterior thalamic radiation, forceps minor, superior longitudinal fasciculus, inferior frontal-occipital fasciculus, inferior longitudinal fasciculus and corticospinal tract. However, these studies reported different brain regions involved in various types of depression.[20–23] For patients with drug-naïve, first-episode MDD in the current study, we obtained the activation of the whole brain through the simulation analysis. Then, we conducted calculations on electric fields for each brain region.

The possible explanations for our findings may be associated with various factors. First, as a conductor, the head has different brain tissues with various conductive properties.[17] The scalp and skull consume electric energy, and some electric energy directly travels from the forehead, stimulating the sites of both mastoid regions from the head surface. Second, electric energy provided by the extracranial currents can directly stimulate the intracranial areas.[10] The more significant the electric field in the brain area near the stimulation electrode, the more energy it can receive, suggesting that the closer the stimulation electrode is to the target area, the more directly it can cause the maximum change in the electric field in that brain area, thus helping to achieve better clinical results of tACS intervention for drug-naïve, first-episode MDD and treatment-resistant depression.[5 7] Third, the CSF also affects the distribution of electric fields; the brain area close to the CSF has a significant electric field due to CSF's high conductivity.[17] Finally, different stimulation electrode positions, frequencies and currents are related to distinct clinical effects on tACS procedures in various studies.[5 11] The frontal lobe, temporal lobe, occipital lobe, parietal lobe, hippocampus,[24] amygdala, cingulate, thalamus, hypothalamus, cerebellum[25] and brainstem were reported to be linked to depression.[26] However, no study on tACS stimulating these brain regions at the same time to intervene for depression has been reported.[8] Our simulation demonstrated that these brain regions in our previous reports were simultaneously stimulated in participants with depression, which may be a pivotal explanation for understanding the therapeutic benefits and rare side effects of tACS,[5] such as headache, tinnitus aurium, tinnitus cerebri, dizziness, phosphene and stimulation-associated sensation under the electrodes.[5]

There are no clinical research reports on stimulating the cerebellum in the treatment of depression. One study showed that the direct extracranial alternating stimulation of the cerebellum via the active electrode 3 cm lateral to the inion over the left cerebellar hemisphere and the return over the ipsilateral buccinator muscle improved motor skill.[27] The result that the static functional connectivity with the cerebrum is disrupted in patients with MDD implied that the cerebellum may play an indispensable role in modulating depression, but it remains largely unknown.[28]

So far, the brainstem is rarely reported as a direct stimulation site to treat brain disorders from the surface of the head. The brainstem has not attracted wide attention from neuroimaging researchers compared with the cerebral hemispheres and cerebellum due to the problem of functional MRI data acquisition, the basilar artery-induced motion artefacts, and the brainstem nucleus and its subregions not being in the available neuroimaging software, such as FSL, and statistical parametric mapping. Furthermore, the brainstem is also hardly manipulated in humans *in vivo*. However, it is generally believed to produce monoamine neurotransmitters, such as the raphe nucleus and locus coeruleus, which are essential bases for mood.[29]

Limitations

Our study was the first to reveal that brain-wide activation was stimulated via 15 mA tACS in patients with drug-naïve, first-episode MDD, a finding that is beneficial to understanding the underlying mechanism of tACS treatment for depression. Although the simulation analysis produces a way of evaluating the whole picture on which intracranial areas are associated with the 15 mA tACS protocol by using the data from patients with drug-naïve, first-episode MDD, it is difficult to measure the precise actions in patients, making it difficult to compare the outcomes of tACS treatment and brain-wide activation. Meanwhile, we only enrolled patients with first-episode major depression. We cannot know how influences from the electric field distribution on the brains of those with other forms of depression or other mental disorders would differ.

Furthermore, there were also some technical limitations in our analysis. The upper limit value of the current in SimNIBS is 2 mA, which is much lower than the 15 mA in our study. Thus, based on our former findings, we modelled the 15 mA effect by scaling proportionally.[10] Although the simulation analysis produces a way of evaluating all of the intracranial areas associated with the 15 mA tACS protocol, it is difficult to measure the precise action in patients with depression. The real relationship between the actual episode of illness and the simulation activation needs further investigation. Also, the different stimulation frequencies, such as 10, 40 or 77.5 Hz, applied in various studies cannot be addressed by the SimNIBS tool.[5 11] They may play a role in the effect of 15 mA tACS on the brain, but they were not currently considered.

Despite these limitations, the simulation analysis still appears to be the optimal method to explore whether specific brain regions, such as the cerebellum and brainstem, are involved in the treatment of 15 mA tACS for depression and other brain disorders.

Implications

To our knowledge, the current simulation study was the first to map the entire brain to identify which brain areas are affected by the stimulation of 15 mA tACS in patients with drug-naïve, first-episode major depression. Interestingly, visualisation of the simulated electric field in our study revealed that multiple brain structures, including the cortex, subcortex, cerebellum and brainstem, were involved in showing the effects of 15 mA tACS, at least among the participants of our study who presented with first-episode major depression. These brain structures may contribute to the mechanisms of 15 mA tACS in depression treatment. Moreover, our results suggest that there may be abnormal functional connectivity in these brain regions and their connections to other brain sites, which in turn could underlie corresponding depressive symptoms. Future studies should explore why the 15 mA tACS procedure seems mechanistically linked to multiple brain structures simultaneously, especially the cerebellum and brainstem, in subjects with drug-naïve, first-episode MDD.

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Correction notice This article has been corrected since it was first published. Figure 1 has been updated.

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Contributors HongxingW designed the experiments. HongxingW, WZ, HuangW, HL, QX, MP, BM, XJ and LT collected clinical data. HongxingW did an analysis. JW did MR data. HongxingW drafted the manuscript. JW, HuangW, KG and HongxingW revised the manuscript for intellectual content. JW and HongxingW accepted full responsibility for the work, supervised the study, had full access to data, and controlled the decision to publish. All authors approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Xuanwu Hospital, Capital Medical University (approval number: LXS (2017) 002-Amendment 1). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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Supplemental materials

Table S1. Baseline demographics and historical characteristics of the enrolled patients

Demographic information	**Patients (n=8)**
Age at enrollment, years, mean (SD)	45.3 (12.2)
Age at onset, years, mean (SD)	43.4 (12.2)
Duration, months, median (IQR)	18.0 (10.8, 36.0)
Sex (%)	
Female	8 (100.0)
History of surgery (%)	2 (25.0)
Education, n (%)	
Junior high school and below	3 (37.5)
High school	2 (25.0)
Over high school	3 (37.5)
Occupation, n (%)	
Employed	5 (62.5)
Unemployed or retired	2 (25.0)
Others	1 (12.5)
HDRS-17 score, mean (SD)	
Total	20.4 (1.9)
Somatic anxiety	7.3 (0.8)
Psychic anxiety	4.4 (0.5)
Core depressive symptoms	6.5 (0.7)
Anorexia	1.1 (0.9)
Suicide	0.5 (0.5)
Genital symptoms	0.6 (0.9)

Note: SD, standard derivation; IQR, interquartile range; HDRS-17, 17-item Hamilton Depression Rating Scale.

Supplemental figure S1. The one-circle of intracranial electrical activity induced by 77.5 Hz, 15 mA tACS.-***Note: Please see the raw figure from the 'gif' file in the supplemental material***.