J. Integr. Sci. Technol. 2022, 10(1), 1-10 Review

Journal of Integrated
SCIENCE & TECHNOLOGY

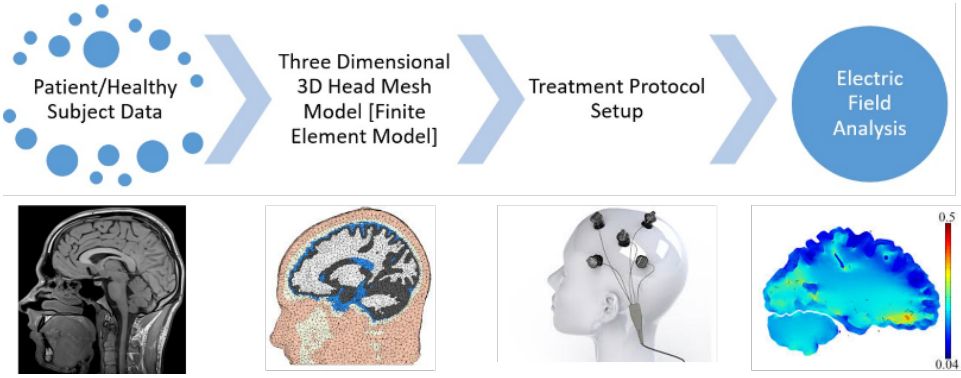
Review of computational approaches to model transcranial direct current stimulations tDCS and its effectiveness

Utkarsh Pancholi,[1*] Vijay Dave[2]

[1]Department of Biomedical Engineering, L.D. College of Engineering, Gujarat Technological University, Ahmedabad-380015, India. [2]Department of Biomedical Engineering, Government Engineering College, Gujarat Technological University, Gandhinagar-382028, India.

Received on: 12-01-2022, Accepted and Published on: 24-Feb-2022

ABSTRACT



Neurological and psychological disorders are being treated by health professionals using medical technologies including drug therapy, electrical stimulation, and psychotherapy in some cases. Because of side effects caused by required drugs and social stigma for psychotherapy, these techniques have some limitations for their applicability in Mild cognitive impairment (MCI), Alzheimer's disease (AD), Huntington disease (HD), dementia, major depressive disorder (MDD) and related neurological abnormalities. Transcranial direct current stimulation is a non-invasive brain stimulation (NIBS) technique that uses small currents to alter characteristics of a healthy and diseased neuron. Even though sophisticated tDCS devices are being used for treatment, treatment protocol and its efficacy is still a debatable question. Researchers have found ways to model tDCS computationally to know the outcome of treatment. This review provides details of computational approaches used to model tDCS. We have reviewed clinical and computational practices carried out by researchers to model treatment modality for tDCS.

Keywords: *Electric field modelling, Neurological diseases, Computational approaches, Magnetic resonance imaging.*

INTRODUCTION

Every cell of the human body has a life cycle and so ageing. With ageing, cognitive and other bodily functions start declining. For the nervous system, it is more challenging to withstand normal actions, the body is having in the early years of the age. Ageing causes drastic changes in daily life whether it is walking, speaking, remembering, seeing, smelling, touching, or experiencing external and internal alterations. There are more than 600 neurological disorders and abnormalities but few are majorly reported diseases like mild cognitive impairment (MCI), Alzheimer's disease (AD), Huntington disease (HD), dementia, major depressive disorder (MDD), Parkinson's disease (PD), muscular dystrophy, brain tumors, and central nervous system injury. Any disease must be diagnosed and treated by medical specialists in the early stage of onset to avoid progression and further complications. World health organization found low-income countries are having only 0.1 neurological assistance or workforce which includes physicians and surgeons per 100000 of population and for high-income countries, it is 7.1 per 100000 of the population.[1]

Dementia and depression are the most common diseases reported in today's time which addresses both old and young age group of people. As the actual cause of Alzheimer's and related dementia

*Corresponding Author name: Utkarsh Pancholi, Department of Biomedical Engineering, L.D. College of Engineering, Ahmedabad-380015, India
Tel: +91-9099757203
Email: utkarshpancholi6387@gmail.com

Cite as: *J. Integr. Sci. Technol., 2022, 10(1), 1-10.*

 Published by: ScienceIN ISSN: 2321-4635
http://pubs.iscience.in/jist

have not been found medically, treatment options are under research.[2,3] For the treatment, drugs and electrical stimulation are being used but conventional drug therapy is having many side effects and long-term drug dependence. As a result, non-invasive electrical brain stimulation has been evolved as an effective treatment alternative for drug-resistant patients. Electro-convulsive therapy (ECT), transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), and transcranial direct current stimulations (tDCS) are currently used in non-invasive treatment modalities for neuromodulation and rehabilitation purposes. In some mental conditions like severe psychosis, schizophrenia, bipolar disorder, and clinical depression, ECT has been considered as the last treatment option where other treatments modalities have not shown any positive effects. There are many short-term and long-term side-effects like nausea, confusion, headache, epilepsy, dementia, and change in personality after the administration of therapeutic current to the patients, even though ECT has been considered as a safe and non-invasive treatment for many neurological disorders.[4] Porter et al. reviewed cognitive side effects of ECT like the inability to learn new things and other cognitive functions while discussing possible monitoring methods.[5] Transcranial magnetic stimulation or Repetitive transcranial magnetic stimulation (rTMS) is another non-invasive treatment modality that delivers repetitive magnetic pulses on the scalp surface to modulate the behavior of nerve cells. With the advantage of painless administration of magnetic pulses to the targeted region, TMS still deals with the common side-effects of tingling, light-headedness, scalp discomfort at the site of treatment, and headache.[6,7] Vagus nerve stimulation is another approach to treat depression, epilepsy, and pain-related abnormalities which can be used for drug-resistant or treatment-resistant (Failed to show positive signs upon ECT or medication) patients. But the efficacy of the therapy is still debatable when used as a monotherapy compared to drug therapy.[8]

Transcranial direct current stimulation is gaining popularity among neuroscientists and psychologists to alter neural function in healthy and diseased populations. It is the only technique that uses very low direct current to modulate neural activity for excitation and inhibition. Many scientists, engineers, and clinicians are trying to investigate the role of tDCS in diseases like epilepsy, schizophrenia, major depressive disorder, Alzheimer's disease, and other common dementia in young and aged people. With the current ranging 1-2 milliampere (mA) applied on a scalp, excitation and inhibition of neural tissue can be achieved using two or multiple electrodes through anodal and cathodal stimulation respectively. Even though the effects of tDCS in healthy and diseased patients are promising, an overall study of stimulation and its effects require a simulation tool as an outcome of treatment varies with individual anatomical differences.[9] With the simulation tool, stimulation parameters, individual head anatomy, and abnormalities can be modelled to check the variation of an electric field within the target brain tissue. Further, generated electric field strength can be considered to estimate the efficacy of selected treatment protocols and their changing behavior upon changing stimulation parameters.

Simulation study might be as simple as solving a three-variable mathematical equation i.e. Ohm's law, V= IR to many complex interdependent processes like forecasting entry of space-shuttle in the space. Criteria for simulation of any process is to have a large set of information to recapitulate the actual experiments. With the advancement in computational capabilities and mathematical representations, it is quite possible to model anatomical and physiological aspects of the human body to do various experiments. As tDCS and other related treatment modalities have limitations for accurate delivery of current and generated electric field distribution with a current emitting device, it is necessary to simulate first with some commercially available or customizable simulation platforms. Danish Research Centre for Magnetic Resonance (DRCMR) and the Technical University of Denmark (DTU) has developed Simulation of Non-invasive Brain Stimulation (SimNIBS) to model electric field generated upon tDCS and TMS stimulation. To model tDCS with the thickness of brain tissue, CSF, skull, scalp, and their conductivities, Parra Lab, Biomedical Engineering Department, City university of New York has developed simple MATLAB-based software called SPHERES. There is also a free web-based tool available to analyze brain stimulations with a simulation called 'Bonsai' developed by Mathias Hueber. A fully automatic Realistic, Volumetric approach to simulate transcranial electrical stimulation (ROAST) is an

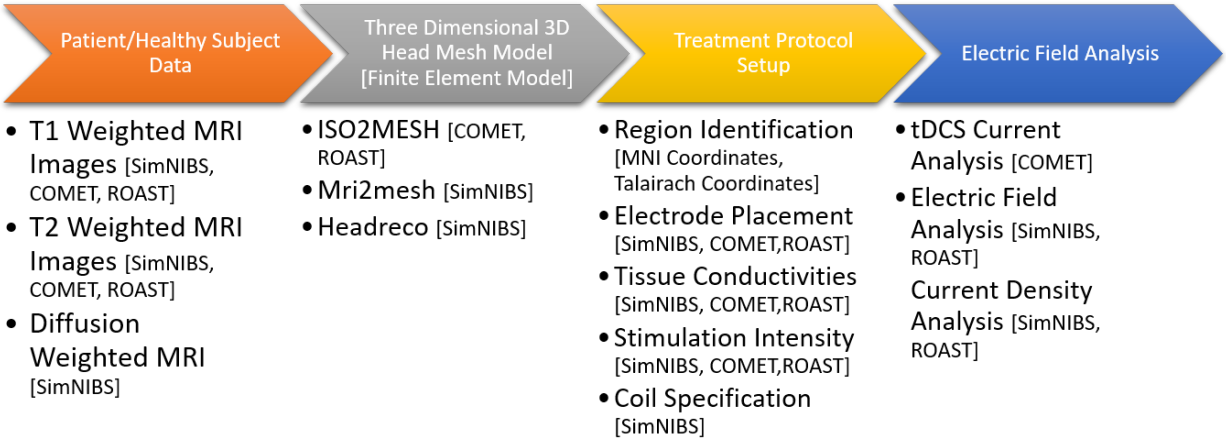


Figure 1: Process diagram for simulation of transcranial electrical stimulation

image-assisted freeware software available to analyze transcranial electrical stimulation. Korea Brain Research Institute, Dongseo University, Hanyang University have developed Computation of Electric field due to Transcranial current Stimulation (COMETS) which is MATLAB assisted toolbox to simulate electric fields generated locally upon tDCS. All these software and simulation platforms have selectively common methodology to create stimulation outcomes of treatment. In this paper, we focus on generalized steps to simulate tDCS treatment with available software. Comparative analysis has been done for their associated tools.

Table 01: Analysis of various freeware computational platforms

Comparative analysis of various computational approaches					
Simulation platform	**Modeling processes**				
	Segmentation of structural MRI	**Conductivity assignment**	**Placement of virtual stimulation electrodes**	**3 Dimensional mesh generation**	**Finite element solver**
SimNIBS	Y	Y	Y	Y	Y
ROAST	Y	Y	Y	Y	Y
COMET	Y	Y	Y	Y	Y
BONSAI	N	N	Y	N	N
SPHEARES	N	Y	Y	Y	Y
	System requirement				
SimNIBS	**Operating system:** Windows-based: Windows-7 & 10, Linux based: Ubuntu 16.04, 18.04 and CentOS 7**,** macOS: 10.13 (High Sierra) **Hardware:** Minimum 6GB RAM and 8GB for optimum performance, holds 3 GB space **Software dependencies:** MATLAB, FSL, Freesurfer				
ROAST	**Operating system:** Windows-based: Windows-7 & 10 **Hardware**: Intel i3 or higher, 4 GB RAM or higher, ≥ 50 GB to run NEWYORK HEAD **Software dependencies:** MATLAB				
COMET	**Operating system: Windows-based:** Windows-7 & 10 **Hardware**: Intel i5 or higher, 8 GB RAM (dependent on mesh size) or higher **Software dependencies:** MATLAB				
BONSAI	**Web-based application (Runs on typical system configuration)**				
SPHERES	**Runs on typical system configuration, Software dependencies:** MATLAB				

METHODOLOGY

To create a simulation for electric field generated upon tDCS stimulation, a systematic computational approach should be adopted. Figure 1 shows a process diagram for simulation of transcranial electrical stimulation which includes tDCS, tACS, and tMS therapeutic modalities. To begin the simulation process medical image is required to identify structural and functional information for the patient. Magnetic resonance imaging (MRI) images are generally available digitally on the internet in Digital Imaging and Communications in Medicine (DICOM) format which needs to be converted in appropriate file format i.e. NifTI format for further processing of segmentation. To create a three-dimensional head mesh for a patient or healthy subject T1 weighted, T2 weighted and diffusion-weighted structural images are required. SimNIBS, COMET, and ROAST have the functionality to process T1 and T2 weighted structural MRI images while diffusion-weighted MRI images can be processed with SimNIBS. T1 weighted structural MRI images highlight fat tissues within the body while fat and water both can be highlighted using T2 weighted images with specific radiofrequency pulse sequence. Diseased tissues have more water and fluid content like cerebrospinal fluid (CSF) than normal tissues so T2 weighted images are best suited for abnormal tissues to be highlighted bright.[10,11] The rate of water diffusion at each voxel of the image can be best characterized by diffusion-weighted MRI images to model grey and white matter for anisotropic conductivities.[12] To create a finite element mesh from acquired or fetched MRI head images, each voxel needs to be assigned a specific tissue class i.e. grey matter, white matter, CSF, skin, and skull. Mri2mesh utilizes two software packages FSL[13,14] and Freesurfer[15] to segment head tissues specifically FSL for extra-cerebral tissues and Freesurfer for surface reconstruction of grey matter.[16] Iso2mesh is another freely available MATLAB-based 3D finite element tetrahedral mesh generation software supported by COMET and ROAST to create meshes from segmented volumetric MRI images.[17,18] More accurate head meshes can be generated with Statistical Parametric Mapping (SPM)[19] based headreco tool supported by SimNIBS.

Region Identification: Cerebral excitability changes through the direct current applied to the various parts of the cortex by targeting specific neurons with current direction as one of the considerations. The direction of current and its density distribution greatly depends on the relative electrode position of both cathode and anode. Placement of electrodes can be configured in three different manners 1) Bi-cephalic, 2) Mono-cephalic and 3) Non-cephalic.[20] Bi-cephalic montage or electrode pair is having two active electrodes, one on a specific position of the head depending on a target and another as a second or reference electrode on a different position on a head. Mono-cephalic montage contains one active electrode as an anode or cathode and a reference electrode on a neck, inion, shoulders, or deltoid muscle. Non-cephalic montage refers to stimulation to non-cortical areas with one active electrode (anode or cathode) on a head and a reference electrode on a non-cortical area. Again placement of active electrode depends on the brain area to be stimulated with tDCS for excitation or inhibition. The location of the electrode on a head is decided by 10-20 or 10-10 electrode placement method usually adopted to measure the electrical activity of the brain.[21] Again the selection of electrodes is based on which activity needs to be addressed. For example, if the concern is language or memory one might stimulate frontotemporal lobes.[22]

Table 02: Region selection with anode and cathode electrode combination in a clinical study.

Selection for clinical study (For neurological and psychiatric disorders)			
References	**Anodal electrode**	**Cathodal electrode**	**Corresponding brain area**
Mild cognitive impairment (MCI)			
J. Kim et al. [23]	F3	F4	Dorsolateral prefrontal cortex (DLPFC)
P.C. Gonzalez et al. [24]	F3	Brachioradialis muscle	Left Dorsolateral prefrontal cortex (LDLPFC)
C. Krebs et al. [25]	F3	Right supraorbital area	LDLPFC
Stonsaovapak C et al. [26]	F4	left supraorbital area	Right Dorsolateral prefrontal cortex (RDLPFC)
M.R.L. Emonson et al.[27]	F3	Fp2	LDLPFC
Alzheimer's disease (AD)			
Lorenzo Pini et al. [28]	P4-P6	supraorbital area	Right inferior parietal
D. Smirni et al. [29]	Contralateral shoulder	F3/F4	Right or left DLPFC
M. Bystad et al. [30]	T3	Fp2	Temporal lobe
Jovana Bjekić et al. [31]	F3-F4	Contralateral cheek	DLPFC
Inagawa T, et al. [32]	F3	Fp2	DLPFC
Major depressive disorder (MDD)			
M. Rezaei et al. [33]	F3	F8	DLPFC
R. Woodham et al. [34]	F3	Fp2/F4/F8	DLPFC
Carvalho et al. [35]	F3	F4	DLPFC
S.N. Vigod et al. [36]	F3	F4	DLPFC
Welch et al. [37]	F3	F4	DLPFC
Parkinson's disease			
Beretta et al. [38]	C3/C4	Contralateral supraorbital area	Primary motor cortex
Nascimento et al. [39]	Cz	Contralateral supraorbital area	Supplementary motor area (SMA)
H. Hadoush et al. [40]	FC1-FC2	Left and right supraorbital area	Primary motor cortex and DLPFC
A. Alexoudi et al. [41]	Cz	Mastoid	SMA
A. Schoellmann et al. [42]	C3	Fp2	Left sensorimotor – Right frontal

Table 03: Region selection with anode and cathode electrode combination in a simulation study.

Selection for simulation study (For neurological and psychiatric disorders)			
References	**Anodal electrode**	**Cathodal electrode**	**Corresponding brain area**
Mild cognitive impairment (MCI)			
Shirin Mahdavi et al. [43]	T3/F3	Supraorbital area	Temporal lobe/Frontal lobe
James Ashcroft et al. [44]	F3	F4	Frontal lobe
Si Jing Tan et al. [45]	F3-F4	Supraorbital area	LDLPFC
Dong-Woo Kang et al. [46]	F3	Right supraorbital area	DLPFC
Alzheimer's disease (AD)			
J.J. Im et al.[47]	F3	F4	DLPFC
K.T. Jones et al. [48]	F4-P4	Contralateral cheek	Right prefrontal cortex-posterior parietal cortex
D. Antonenko et al. [49]	F3/C3/P3	Fp2/ P3/ F4/ P4	Frontal and parietal lobes
A. Indahlastari et al. [50]	F4-C3	F3-Fp2	Frontal lobe
Utkarsh Pancholi et al. [51]	F3	Fp2	LDLPFC
Major depressive disorder (MDD)			
Paulo J. C. Suen et al. [52]	F5	F6	DLPFC
Nya Mehnwolo Boayue et al. [53]	F3	F4	LDLPFC
G. Csifcsák et al. [54]	F3/Fz	F4/Right supraorbital (RSO) /F8	LDLPFC/Medial prefrontal cortex
Eva Mezger et al. [55]	F3	F4	LDLPFC
Laura Santos et al. [56]	F3	RSO	DLPFC
Parkinson's disease			
J.-H. Kim et al. [9]	F3	Fp2	DLPFC
Kevin Caulfield et al. [57]	C3	C4/Fp2	Primary motor cortex

Tissue conductivities: Choice of the MRI scan (T1 weighted or T2 weighted) helps to distinguish between soft tissue and hard tissue i.e. one with the highest conductivity and the other with the lowest conductivity. T1 weighted scans describe both the hardest and softest tissue similar on brightness scale i.e. skull and CSF appears dark whereas T2 weighted scan defines both the tissue on an opposite brightness scale i.e. skull appears dark and CSF as a bright [16]. Being a dense tissue skull has high resistivity results in lowest conductivity and CSF has a low resistivity with the highest conductivity among the head tissues. For finite element meshing, segmented MRI images have to be converted into the head mesh where each voxel is assigned to a specific tissue class. Also to distinguish among the electric field to be generated after stimulation, each tissue should be identified by different conductivities values. For the simulation, purpose researchers use conductivity values reported in literature derived from in-vivo or in-vitro experiments, as shown in Table 04.

Table 04: Conductivity values for corresponding head tissue.

Tissue name	Conductivity values (S/m)
White matter	0.126 [58],
Gray matter	0.275 [58]
CSF	1.654 [58]
Bone	0.01 [58]
Scalp	0.465 [58]
Eyes	0.5 [59]
Silicone rubber	29.4 [60]
Saline	1.0 [61]

Co-ordinate system: Co-ordinates represent multiple information of a single point i.e. relative location, explication of three axes (In three-dimensional coordinate system), and measurement unit of a numerical representation. To identify various anatomical and functional locations on a human brain, Talairach and Tournoux dissected an individual human brain and defines a co-ordinate system using anterior and posterior commissure as a reference.[62] Although Talairach and Tournoux have invented a way to locate the site on the human brain with anterior commissure as an origin, represented by (0, 0, 0) at origin, it is limited with a single subject. In Electroencephalography (EEG) co-ordinate system is defined by anatomical landmarks associated with left pre-auricular (LPA), right pre-auricular (RPA), inion, and nasion. But for MRI images where data is in a 3-dimensional form voxels representation in [3×1] matrix i.e. (x,y,z) where x, y, and z represents (1,1,1) as a first voxel and (256,256,256) as the last voxel.

Stimulation intensity: Effects of tDCS on targeted brain areas varies upon multiple stimulation parameters in which current intensity is a prime consideration. When applied with available market-based stimulation tDCS devices, other parameters can be fixed i.e. electrode size and shape while treating the patient but the current intensity is only variable. Based on research and current knowledge of the intensity of the stimulation, 1 to 2 mA is considered to be a safe range for treating neurological disease

Table 05: Details of co-ordinate systems with their origin and orientation

Co-ordinate system	Origin	Orientation	Unit
Anterior commissure posterior commissure (ACPC)	Anterior commissure	Right anterior superior (RAS)	mm
DICOM	Centre of MRI gradient coil	Left posterior superior(LPS)	mm
Freesurfer	Center of isotropic 1 mm 256x256x256 volume	RAS	mm
Montreal Neurological Institute (MNI)	Anterior commissure	RAS	mm
Talairach-Tournoux	Anterior commissure	RAS	mm

Table 06: Area of the cortical and sub-cortical regions and their corresponding Talairach and MNI coordinates [63].

Area	Talairach co-ordinate	MNI co-ordinate
Left DLPFC	(-38, 34, 34)	(-39, 34, 36)
Right DLPFC	(34, 39, 30)	(35, 38, 31)
Right amygdala	(20, -4, -15)	(21, -1, -22)
Left amygdala	(-24, -3, -15)	(-24, 0, -22)
Right hippocampus	(27, -23, -8)	(28, -22, -15)
Left hippocampus	(-28, -20, -9)	(-30, -19, -15)
Right hypothalamus	(2, -3, -6)	(3, -1, -11)
Left hypothalamus	(-4, -4, -6)	(-4, -2, -11)
Right thalamus	(9, -20, 8)	(10, -20, 5)
Left thalamus	(-8, -18, 8)	(-9, -17, 6)
Right primary motor cortex	(38, -15, 42)	(38, -18, 45)
Left primary motor cortex	(-36, -17, 44)	(-36, -20, 48)
Right primary sensory cortex	(41, -24, 44)	(41, -27, 47)
Left primary sensory cortex	(-40, -25, 44)	(-40, -28, 47)

patients and enhancement of existing cognitive capabilities in healthy individuals.[64] Even though fixation of stimulation of current between this range, effects can be varied upon electrode placement, the orientation of the electrode upon a cortical surface (Alignment of neurons while current propagation), tissue conductivities, physiological condition, and other anatomical differences like size and shape of the head tissues. All these considerations intend to achieve adequate electric field in a precise location in a deep or superficial structure of the stimulated brain. Vöröslakos et al.

measured electric fields with intracellular and extracellular recordings in rats and found minimum 1mV/mm potential difference is required to alter neuronal membrane characteristics.[65] For that current intensities need to be increased sufficiently up to 4 to 6 mA, but no experiments have been done to date because of the doubtful effects on brain tissues considering an alternating current or direct current. In line with the current intensity, how long direct current is being delivered to the brain also matters. Also, after-effects can be acknowledged using manual methods used to trace cognitive enhancement and working memory improvements.[66] However, computational modelling of tDCS and its effects focuses only on instantaneous generation of electric fields. Variation in the electric field based on duration of the stimulation is not a part of simulation tools. SimNIBS, COMETS, BONSAI, ROAST and spheres supports variability of current intensity to visualize change in electric field on a ROI.

Table 07: Selection of current intensity for clinical studies with intended study and its outcome.

Selection of current intensity (Clinical studies)				
Reference	**Current intensity**	**Target brain area**	**Study**	**Outcome**
Y. Tu, J. Cao, S. Guler et al. [67]	2 mA	Anodal: RDLPFC Cathodal: Left orbitofrontal cortex (LOFC)	To know the modulatory effects of tDCS on brain dynamics using fMRI.	tDCS induced neural excitability can modulate brain dynamics visible in fMRI.
Vahid Nejati et al. [68]	1 mA	Anodal: LDLPFC Cathodal: ventromedial prefrontal cortex (vmPFC)	Reward processing phenomenon in attention deficit-hyperactivity disorder (ADHD).	Improves tendency to take more conservative decisions in ADHD patients.
C.M. Sadler et al. [69]	1 mA	Anodal: SMA	Limb kinematics in Parkinson's disease (PD).	Improved movement kinematics of an upper limb using simple RT task in PD's patients.
Chong Zhao et al. [70]	2 mA	Anodal: T3/T4 Cathodal: Ipsilateral cheek	Memory recognition upon visual search	tDCS can alter the brain plasticity underlying the targeted tissue.
F. Grami et al. [71]	1.5 mA	Anodal: Right posterior cerebellar hemisphere Cathodal: Left acromion	Effect of tDCS on motor function.	tDCS modulates cognitive brain networks controlling motor execution and mental imagery.

Table 08: Selection of current intensity for simulation studies with intended study and its outcome.

Selection of current intensity (Simulation studies)				
Reference	**Current intensity**	**Target brain area**	**Study**	**Outcome**
Gaurav V.Bhalerao et al. [72]	2 mA	Anodal: AF3 Cathodal: Cp5 (Frontotemporal area)	Comparison of various tDCS simulation platforms for a given stimulation.	Different computational approaches give varying electric field distribution and other insight for the same stimulation protocol.
Ainslie Johnstone et al. [73]	1 mA	Anodal: Left primary motor cortex (M1) Cathodal: Right supraorbital ridge	Effect of brain-lesions on electric field strength (E-field) upon tDCS.	Brain-lesions have greatly impacted E-field magnitude up to 30% compared with normal tissues.
Molero-Chamizo, A et al. [74]	1-2 mA	Anodal: Left primary motor cortex (M1), C3 according to 10-20 EEG placement method. Cathodal: Right supraorbital region. Fp2 according to 10-20 EEG placement method.	To find the limitation of two computational approaches SimNIBS and COMETs.	Both the approaches gave similar results with minimum deviation in generated E-field magnitude.
Paulo J. C. Suen et al. [52]	2 mA	Anodal: F5 Cathodal: F6 (Frontal lobe)	E-field variability in depression.	E-field strength is associated with behavioral changes in depressed patients.
Utkarsh Pancholi et al. [75]	1 mA, 1.25 mA, 1.50 mA, 1.75 mA and 2 mA	Anodal: F3 Cathodal: Fp2 (Frontal lobe)	E-field strength calculation in AD and MCI patients.	The strength of an electric field increases linearly with an increase in applied current intensity in AD and MCI patients keeping other simulation parameters constant.

Electric field analysis: Electric field analysis focuses on three parameters, 1) Electric field strength (in V/m), 2) Direction of the electric field (Direction of the current flowing through the electrodes parallel or perpendicular to the neurons positioned in a cortical target) and 3) Focality of the electric field (Higher in multiple electrodes with low intensity and lower in bipolar electrodes with high intensity).[76,12] Advancement in computational models facilitating analysis of electric field in various brain tissues like skull, skin, CSF, white matter, and gray matter.[75] The electric field can be calculated by solving a mathematical equation $\vec{E} = -\nabla\varphi$, where $\vec{E}$ is an electric field vector and φ is an electric potential.[59] Lee et al. discussed the relationship between intensity and focality where bipolar montages can develop high electric field strength with low focality and multi-electrode high definition-transcranial direct current stimulation (HD-tDCS) (4×1) montage can be more focused with less electric field.[76] The probability of depolarization and hyperpolarization is generally characterized by the orientation of input direct current upon the neuronal position. If the direction of the input current is radial, it is more likely to have a polarization within the cell and so is the excitation and inhibition. Figure 02 (C) is showing a pictorial representation of the current direction in the gyri and sulcus. Where the alignment of neuronal cells decides polarization effects. If the current direction is towards the soma from dendrites there is excitation and so is depolarization whereas hyperpolarization or inhibition occurs if the current direction is towards dendrites from soma Figure 02 (A & B). Collectively there are three possibilities 1) Depolarization (If the current is radially inward) Figure 03 (C) 2) Hyper-polarization (If the current is radially outward) Figure 03 (D) and 3) Minor to no polarization (If the current is tangential) Figure 03 (E).

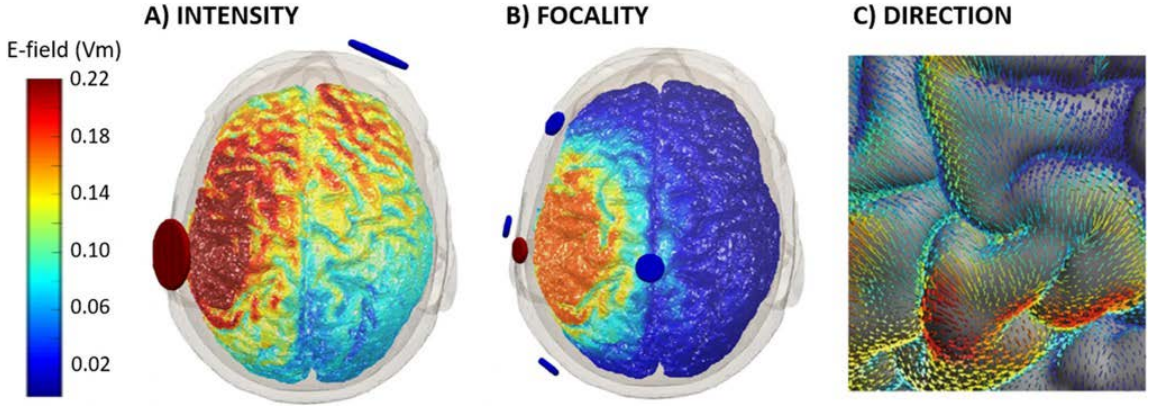


Figure 02: E-field in various montage selection A) Bi-polar configuration with increased E-field intensity B) Multi-polar HD-tDCS montage with increased focality and less E-field strength C) Direction of E-field on gyrus and sulci (Image A and B taken from J. S. A. Lee et al. [76], Image C taken from Saturnino et al. [16])

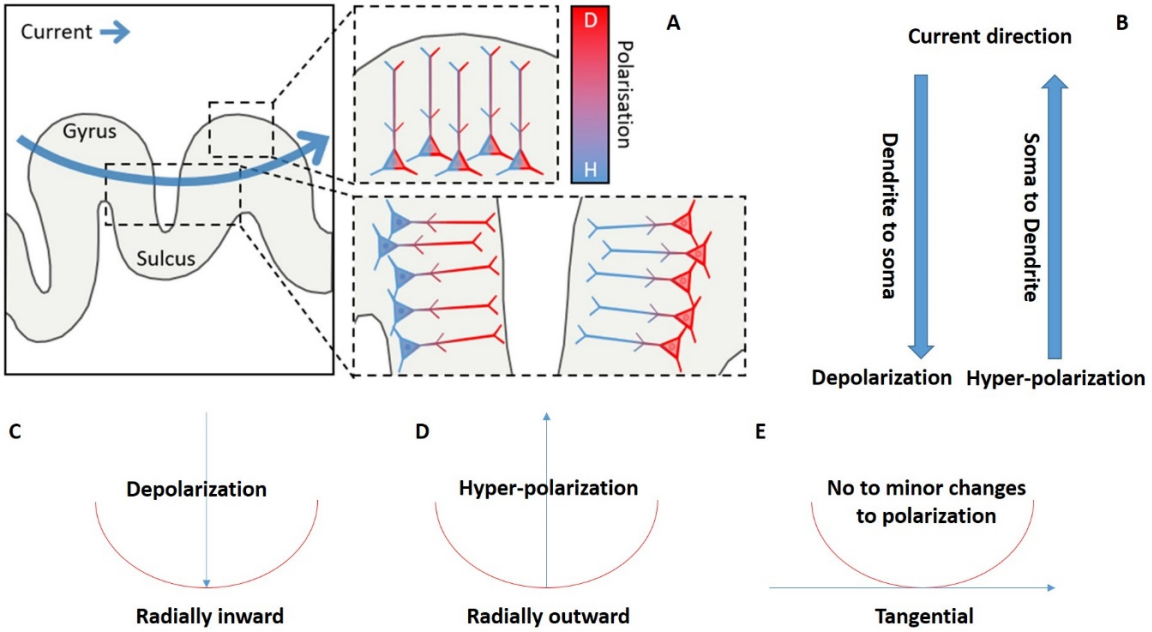


Figure 03: Effect of applied direct current on neuronal alignment and orientation. Depolarization occurs upon the current direction radially inward (C) (from dendritic region to somatic region (B)) and hyperpolarization occurs upon current direction radially outward (D) (from somatic region to dendritic region (B)). There are null to minor changes in polarization upon the tangential direction of applied direct current (E). (Image A taken from J. S. A. Lee [76])

Table 09: Measured electric field strength in recent studies with selected simulation parameters.

Reference	Study	Anode	Cathode	Current intensity (mA)	E-field strength (V/m)
D. Antonenko et al. [77]	E-field variability upon different head circumferences	C3	Supraorbital region	Anodal: 1.0	0.15 to 0.23
		F3	F4	Cathodal: -1.0	
		P3	P4		
		P4	Supraorbital region		
Kevin A. Caulfield et al. [78]	Effect of optimizing stimulation parameters on targeted cortical sites i.e. electrode size and position.	C3	C4	2	0.271
		C3	Fp2	2	0.273
Utkarsh Pancholi et al. [51]	Quantification of electric field strength in AD and MCI patients upon tDCS.	F3	Fp2	Anodal: 1.75	0 to 0.348 (MCI)
				Cathodal: -1.75	0 to 0.328 (AD)

LIMITATIONS

Computational tools for tDCS are intended to mimic the current distribution and electric field generation with all possible simulations of treatment protocols. With all available specialized tools, it has been possible to analyze the effects of tDCS on a targeted area of the brain. There are several limitations while analyzing the finite element model generated with computational approaches i.e. 1) Head model is generated based on anatomical information gathered with T1 or T2 weighted images and not having any physiological information associated with the current state of the brain while simulation. 2) Focality and electric field strength differ opposite to each other i.e. increased focality can be achieved at a cost of decreased electric field strength and electric field strength can be increased at a cost of decreased focality. 3) Current direction can be set radially in with tools but neuronal alignment is unknown so it is difficult to address which region is being depolarized or hyperpolarized. 4) Individual anatomical and physiological differences (Morphological and electrical properties) with all other variables like age, gender, and condition of the targeted site change outcome of both stimulation and simulation. 5) It is impossible to generalize treatment protocol with simulation. 6) Optimization of one parameter can be done i.e. electric field strength or focality, all variables have not been considered simultaneously.

CONCLUSION

We have compared various computational approaches with their functionality required to model tDCS treatment protocol. Comparative analysis has been done to identify modelling processes available in computational tools i.e. SimNIBS, COMETS, ROAST, SPHERES, and BONSAI. There are different hardware dependencies for all simulation tools. Region identification for stimulation target can be decided with conventional 10-20, 10-10 electrode placement method. The target location can also be decided with voxel coordinates, subject-specific coordinates, and MNI coordinates. MNI coordinates can be found in a research study for intended targets. Variation in MNI coordinates can be found in different research studies as the values can be overlapping. Tissue conductivities must be selected from standard literature for applying conductivities values to different tissues of the brain. Area of the cortical and sub-cortical regions and their corresponding Talairach and MNI coordinates have been discussed. The selection of current intensity for clinical and simulation studies has been discussed along with the research objective and outcome. Electric field strength and focality are inversely proportional to each other which limits the optimization of one or other parameters for a simulation research study. Different computational tools are having different approaches to model tDCS treatment along with multiple software dependencies. There are no advantages or disadvantages among the available simulation tools rather they can be used according to their functionality and information gathered with the simulation study.

CONFLICT OF INTEREST

Authors declared no conflict of interest.

REFERENCES

1. WHO. Atlas: country resources for neurological disorders 2004. *World Heal. Organ.* **2004**, 71.
2. R. Singh, G. Geetanjali, N. Sharma. Monoamine Oxidase Inhibitors for Neurological Disorders: A review. *Chem. Biol. Lett.* **2014**, 1 (1), 33–39.
3. P. Singh, P.P. Sharma. Medicinal applications of Saffron plant in Neurological disorders. *Chem. Biol. Lett.* **2020**, 7 (4), 242–246.
4. M. Li, X. Yao, L. Sun, et al. Effects of Electroconvulsive Therapy on Depression and Its Potential Mechanism. *Front. Psychol.* **2020**, 11, 80.
5. R.J. Porter, B.T. Baune, G. Morris, et al. Cognitive side-effects of electroconvulsive therapy: what are they, how to monitor them and what to tell patients. *BJPsych Open* **2020**, 6 (3), e40.
6. D. Hett, J. Rogers, C. Humpston, S. Marwaha. Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Depression in Adolescence: A Systematic Review. *J. Affect. Disord.* **2021**, 278, 460–469.
7. J.P. Lefaucheur, A. Aleman, C. Baeken, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). *Clin. Neurophysiol.* **2020**, 131 (2), 474–528.
8. D. Holle-Lee, C. Gaul. Noninvasive vagus nerve stimulation in the management of cluster headache: Clinical evidence and practical experience. *Ther. Adv. Neurol. Disord.* **2016**, 9 (3), 230–234.
9. J.H. Kim, D.W. Kim, W.H. Chang, et al. Inconsistent outcomes of transcranial direct current stimulation may originate from anatomical differences among individuals: Electric field simulation using individual MRI data. *Neurosci. Lett.* **2014**, 564, 6–10.
10. Y. Chen, S.J. Almarzouqi, M.L. Morgan, A.G. Lee. T1-Weighted Image. *Encycl. Ophthalmol.* **2018**, 1747–1750.
11. Y. Chen, S.J. Almarzouqi, M.L. Morgan, A.G. Lee. T2-Weighted Image. *Encycl. Ophthalmol.* **2018**, 1750–1752.

12. G.B. Saturnino, O. Puonti, J.D. Nielsen, et al. SimNIBS 2.1: A Comprehensive Pipeline for Individualized Electric Field Modelling for Transcranial Brain Stimulation. *bioRxiv* **2018**.
13. M. Jenkinson, C.F. Beckmann, T.E.J. Behrens, M.W. Woolrich, S.M. Smith. FSL. *Neuroimage* **2012**, 62 (2), 782–790.
14. S.M. Smith, M. Jenkinson, M.W. Woolrich, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* **2004**, 23 (SUPPL. 1), S208–S219.
15. B. Fischl. FreeSurfer. *Neuroimage* **2012**, 62 (2), 774–781.
16. G.B. Saturnino, O. Puonti, J.D. Nielsen, et al. SimNIBS 2.1: A Comprehensive Pipeline for Individualized Electric Field Modelling for Transcranial Brain Stimulation. *bioRxiv* **2018**, 1–13.
17. A.P. Tran, S. Yan, Q. Fang. Improving model-based functional near-infrared spectroscopy analysis using mesh-based anatomical and light-transport models. *Neurophotonics* **2020**, 7 (01), 1.
18. Q. Fang, D.A. Boas. Tetrahedral mesh generation from volumetric binary and grayscale images. *Proc. - 2009 IEEE Int. Symp. Biomed. Imaging From Nano to Macro, ISBI 2009* **2009**, 1142–1145.
19. W. Penny, K. Friston, J. Ashburner, S. Kiebel, T. Nichols. Statistical Parametric Mapping, 1st ed.; Elsevier, Amsterdam ;;Boston, **2007**.
20. H. Zhao, L. Qiao, D. Fan, et al. Modulation of brain activity with noninvasive transcranial direct current stimulation (tDCS): Clinical applications and safety concerns. *Front. Psychol.* **2017**, 8 (MAY), 685.
21. V. Jurcak, D. Tsuzuki, I. Dan. 10/20, 10/10, and 10/5 systems revisited: Their validity as relative head-surface-based positioning systems. *Neuroimage* **2007**, 34 (4), 1600–1611.
22. A. Gangemi, B. Colombo, R.A. Fabio. Effects of short- and long-term neurostimulation (tDCS) on Alzheimer's disease patients: two randomized studies. *Aging Clin. Exp. Res.* **2021**, 33 (2), 383–390.
23. J. Kim, H. Kim, H. Jeong, D. Roh, D.H. Kim. tACS as a promising therapeutic option for improving cognitive function in mild cognitive impairment: A direct comparison between tACS and tDCS. *J. Psychiatr. Res.* **2021**, 141, 248–256.
24. P.C. Gonzalez, K.N.K. Fong, T. Brown. Transcranial direct current stimulation as an adjunct to cognitive training for older adults with mild cognitive impairment: A randomized controlled trial. *Ann. Phys. Rehabil. Med.* **2021**, 64 (5), 101536.
25. C. Krebs, S. Klöppel, B. Heimbach, J. Peter. Education moderates the effect of tDCS on episodic memory performance in cognitively impaired patients. *Brain Stimul.* **2020**, 13 (5), 1396–1398.
26. C. Stonsaovapak, S. Hemrungroj, P. Terachinda, K. Piravej. Effect of Anodal Transcranial Direct Current Stimulation at the Right Dorsolateral Prefrontal Cortex on the Cognitive Function in Patients With Mild Cognitive Impairment: A Randomized Double-Blind Controlled Trial. *Arch. Phys. Med. Rehabil.* **2020**, 101 (8), 1279–1287.
27. M.R.L. Emonson, P.B. Fitzgerald, N.C. Rogasch, K.E. Hoy. Neurobiological effects of transcranial direct current stimulation in younger adults, older adults and mild cognitive impairment. *Neuropsychologia* **2019**, 125, 51–61.
28. L. Pini, F.B. Pizzini, I. Boscolo-Galazzo, et al. Brain network modulation in Alzheimer's and frontotemporal dementia with transcranial electrical stimulation. *Neurobiol. Aging* **2022**, 111, 24–34.
29. D. Smirni, M. Oliveri, E. Misuraca, et al. Verbal Fluency in Mild Alzheimer's Disease: Transcranial Direct Current Stimulation over the Dorsolateral Prefrontal Cortex. *J. Alzheimer's Dis.* **2021**, 81 (3), 1273–1283.
30. M. Bystad, B. Storø, N. Gundersen, et al. Can accelerated transcranial direct current stimulation improve memory functions? An experimental, placebo-controlled study. *Heliyon* **2020**, 6 (10), e05132.
31. J. Bjekić, M. Živanović, S.R. Filipović. Transcranial direct current stimulation (Tdcs) for memory enhancement. *J. Vis. Exp.* **2021**, 2021 (175), e62681.
32. T. Inagawa, Y. Yokoi, Y. Yamada, et al. Effects of multisession transcranial direct current stimulation as an augmentation to cognitive tasks in patients with neurocognitive disorders in Japan: A study protocol for a randomised controlled trial. *BMJ Open* **2020**, 10 (12), e037654.
33. M. Rezaei, M.M. Shariat Bagheri, M. Ahmadi. Clinical and demographic predictors of response to anodal tDCS treatment in major depression disorder (MDD). *J. Psychiatr. Res.* **2021**, 138, 68–74.
34. R. Woodham, R.M. Rimmer, J. Mutz, C.H.Y. Fu. Is tDCS a potential first line treatment for major depression? *Int. Rev. Psychiatry* **2021**, 33 (3), 250–265.
35. S. Carvalho, Ó.F. Gonçalves, A.R. Brunoni, et al. Transcranial Direct Current Stimulation as an Add-on Treatment to Cognitive-Behavior Therapy in First Episode Drug-Naïve Major Depression Patients: The ESAP Study Protocol. *Front. Psychiatry* **2020**, 11, 563058.
36. S.N. Vigod, K.E. Murphy, C.L. Dennis, et al. Transcranial direct current stimulation (tDCS) for depression in pregnancy: A pilot randomized controlled trial. *Brain Stimul.* **2019**, 12 (6), 1475–1483.
37. E.S. Welch, A. Weigand, J.E. Hooker, et al. Feasibility of Computerized Cognitive-Behavioral Therapy Combined With Bifrontal Transcranial Direct Current Stimulation for Treatment of Major Depression. *Neuromodulation* **2019**, 22 (8), 898–903.
38. V.S. Beretta, R. Vitório, P. Nóbrega-Sousa, et al. Effect of Different Intensities of Transcranial Direct Current Stimulation on Postural Response to External Perturbation in Patients With Parkinson's Disease. *Neurorehabil. Neural Repair* **2020**, 34 (11), 1009–1019.
39. L.R. Nascimento, E.M. Nakamura-Palacios, A. Boening, et al. Transcranial direct current stimulation (tDCS) in addition to walking training on walking, mobility, and reduction of falls in Parkinson's disease: study protocol for a randomized clinical trial. *Trials* **2021**, 22 (1), 1–7.
40. H. Hadoush, M. Al-Jarrah, H. Khalil, A. Al-Sharman, S. Al-Ghazawi. Bilateral anodal transcranial direct current stimulation effect on balance and fearing of fall in patient with Parkinson's disease. *NeuroRehabilitation* **2018**, 42 (1), 63–68.
41. A. Alexoudi, P. Patrikelis, T. Fasilis, et al. Effects of anodal tDCS on motor and cognitive function in a patient with multiple system atrophy. *Disabil. Rehabil.* **2020**, 42 (6), 887–891.
42. A. Schoellmann, M. Scholten, B. Wasserka, et al. Anodal tDCS modulates cortical activity and synchronization in Parkinson's disease depending on motor processing. *NeuroImage Clin.* **2019**, 22, 101689.
43. S. Mahdavi, F. Towhidkhah. Computational human head models of tDCS: Influence of brain atrophy on current density distribution. *Brain Stimul.* **2018**, 11 (1), 104–107.
44. J. Ashcroft, R. Patel, A.J. Woods, et al. Prefrontal transcranial direct-current stimulation improves early technical skills in surgery. *Brain Stimul.* **2020**, 13 (6), 1834–1841.
45. S.J. Tan, H.L. Filmer, P.E. Dux. Age-related differences in the role of the prefrontal cortex in sensory-motor training gains: A tDCS study. *Neuropsychologia* **2021**, 158, 107891.
46. D.W. Kang, S.M. Wang, T.Y. Kim, et al. Impact of transcranial direct current stimulation on cognitive function, brain functional segregation, and integration in patients with mild cognitive impairment according to amyloid-beta deposition and apoe ε4-allele: A pilot study. *Brain Sci.* **2021**, 11 (6), 772.
47. J.J. Im, H. Jeong, M. Bikson, et al. Effects of 6-month at-home transcranial direct current stimulation on cognition and cerebral glucose metabolism in Alzheimer's disease. *Brain Stimul.* **2019**, 12 (5), 1222–1228.
48. K.T. Jones, E.L. Johnson, M.E. Berryhill. Frontoparietal theta-gamma interactions track working memory enhancement with training and tDCS. *Neuroimage* **2020**, 211, 116615.
49. D. Antonenko, U. Grittner, G. Saturnino, et al. Inter-individual and age-dependent variability in simulated electric fields induced by conventional transcranial electrical stimulation. *Neuroimage* **2021**, 224, 117413.
50. A. Indahlastari, A. Albizu, A. O'Shea, et al. Modeling transcranial electrical stimulation in the aging brain. *Brain Stimul.* **2020**, 13 (3), 664–674.
51. U. Pancholi, V. Dave. Quantification of electric field strength of tDCS in alzheimer's and mild cognitive impairment patients. *Int. J. Adv. Technol. Eng. Explor.* **2021**, 8 (82), 1168–1182.
52. P.J.C. Suen, S. Doll, M.C. Batistuzzo, et al. Association between tDCS computational modeling and clinical outcomes in depression: data from the ELECT-TDCS trial. *Eur. Arch. Psychiatry Clin. Neurosci.* **2021**, 271 (1), 101–110.

53. N.M. Boayue, G. Csifcsák, O. Puonti, A. Thielscher, M. Mittner. Head models of healthy and depressed adults for simulating the electric fields of non-invasive electric brain stimulation. *F1000Research* **2018**, 7, 704.
54. G. Csifcsák, N.M. Boayue, O. Puonti, A. Thielscher, M. Mittner. Effects of transcranial direct current stimulation for treating depression: A modeling study. *J. Affect. Disord.* **2018**, 234, 164–173.
55. E. Mezger, B.S. Rauchmann, A.R. Brunoni, et al. Effects of bifrontal transcranial direct current stimulation on brain glutamate levels and resting state connectivity: multimodal MRI data for the cathodal stimulation site. *Eur. Arch. Psychiatry Clin. Neurosci.* **2021**, 271 (1), 111–122.
56. L. Santos, M. Martinho, R. Salvador, et al. Evaluation of the electric field in the brain during transcranial direct current stimulation: A sensitivity analysis. *Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBS* **2016**, 2016-October, 1778–1781.
57. K. Caulfield, M. George. Anterior posterior pad surround (APPS) tDCS for higher electric field intensity and focality in the primary motor cortex - Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation. *Brain Stimulation.* 2021, p P1.096.
58. T.A. Wagner, M. Zahn, A.J. Grodzinsky, A. Pascual-Leone. Three-dimensional head model simulation of transcranial magnetic stimulation. *IEEE Trans. Biomed. Eng.* **2004**, 51 (9), 1586–1598.
59. A. Opitz, W. Paulus, S. Will, A. Antunes, A. Thielscher. Determinants of the electric field during transcranial direct current stimulation. *Neuroimage* **2015**, 109, 140–150.
60. ELASTOSIL® R 570/60 OH | High Consistency Silicone Rubber (HCR) | Wacker Chemie AG https://www.wacker.com/h/en-us/silicone-rubber/high-consistency-silicone-rubber-hcr/elastosil-r-57060-oh/p/000005597.
61. G.B. Saturnino, A. Antunes, A. Thielscher. On the importance of electrode parameters for shaping electric field patterns generated by tDCS. *Neuroimage* **2015**, 120, 25–35.
62. Neurosurgery | Co-Planar Stereotaxic Atlas of the Human Brain https://www.thieme.com/books-main/neurosurgery/product/414-co-planar-stereotaxic-atlas-of-the-human-brain.
63. C.M. Lacadie, R.K. Fulbright, N. Rajeevan, R.T. Constable, X. Papademetris. More accurate Talairach coordinates for neuroimaging using non-linear registration. *Neuroimage* **2008**, 42 (2), 717–725.
64. A.J. Woods, A. Antal, M. Bikson, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clin. Neurophysiol.* **2016**, 127 (2), 1031–1048.
65. M. Vöröslakos, Y. Takeuchi, K. Brinyiczki, et al. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. *Nat. Commun.* **2018**, 9 (1), 1–17.
66. S.J. Westwood, N. Bozhilova, M. Criaud, et al. The effect of transcranial direct current stimulation (tDCS) combined with cognitive training on EEG spectral power in adolescent boys with ADHD: A double-blind, randomized, sham-controlled trial. *IBRO Neurosci. Reports* **2022**, 12, 55–64.
67. Y. Tu, J. Cao, S. Guler, et al. Perturbing fMRI brain dynamics using transcranial direct current stimulation. *Neuroimage* **2021**, 237, 118100.
68. V. Nejati, A. Sarraj Khorrami, M.A. Nitsche. Transcranial Direct Current Stimulation Improves Reward Processing in Children With ADHD. *J. Atten. Disord.* **2021**, 25 (11), 1623–1631.
69. C.M. Sadler, A.T. Kami, J. Nantel, A.N. Carlsen. Transcranial direct current stimulation of supplementary motor area improves upper limb kinematics in Parkinson's disease. *Clin. Neurophysiol.* **2021**, 132 (11), 2907–2915.
70. C. Zhao, G.F. Woodman. Converging evidence that neural plasticity underlies transcranial direct-current stimulation. *J. Cogn. Neurosci.* **2020**, 33 (1), 146–157.
71. F. Grami, G. de Marco, F. Bodranghien, M. Manto, C. Habas. Cerebellar Transcranial Direct Current Stimulation Reconfigures Brain Networks Involved in Motor Execution and Mental Imagery. *Cerebellum* **2021**, 1–16.
72. G. V. Bhalerao, V.S. Sreeraj, A. Bose, J.C. Narayanaswamy, G. Venkatasubramanian. Comparison of electric field modeling pipelines for transcranial direct current stimulation. *Neurophysiol. Clin.* **2021**, 51 (4), 303–318.
73. A. Johnstone, C. Zich, C. Evans, et al. The impact of brain lesions on tDCS-induced electric field magnitude. *bioRxiv* **2021**, 2021.03.19.436124.
74. A. Molero-Chamizo, M.A. Nitsche, C. Gutiérrez Lérida, et al. Standard Non-Personalized Electric Field Modeling of Twenty Typical tDCS Electrode Configurations via the Computational Finite Element Method: Contributions and Limitations of Two Different Approaches. *Biology (Basel).* **2021**, 10 (12), 1230.
75. U. Pancholi, V. Dave. Quantification of electric field strength of tDCS in alzheimer's and mild cognitive impairment patients. *Int. J. Adv. Technol. Eng. Explor.* **2021**, 8 (82), 1168–1182.
76. J.S.A. Lee, S. Bestmann, C. Evans. A Future of Current Flow Modelling for Transcranial Electrical Stimulation? *Curr. Behav. Neurosci. Reports* **2021**, 8 (4), 150–159.
77. D. Antonenko, U. Grittner, O. Puonti, A. Flöel, A. Thielscher. Estimation of individually induced e-field strength during transcranial electric stimulation using the head circumference. *Brain Stimul.* **2021**, 14 (5), 1055–1058.
78. K.A. Caulfield, M.S. George. Optimizing transcranial direct current stimulation (tDCS) electrode position, size, and distance doubles the on-target cortical electric field: Evidence from 3000 Human Connectome Project models. *bioRxiv* **2021**, 2021.11.21.469417.

AUTHOR BIOGRAPHIES

Utkarsh Pancholi is currently an Assistant Professor in the Biomedical Engineering Department, L.D College of Engineering affiliated with Gujarat Technological University. He has done M. Tech from IIT, BHU. Varanasi, India. His area of interest is Computational Neuroscience, Neuromodulation, and Rehabilitation.

Vijay Dave is currently an Assistant Professor in Biomedical Engineering Department, GEC, Gandhinagar, Gujarat affiliated with Gujarat Technological University. He has done M. Tech and Ph.D. from IIT, Mumbai, Maharashtra, India. His area of interest is Computational Neuroscience, Bio-potential Instrumentation and Rehabilitation Technology.