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Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines (2017-2025: An Update)

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Corresponding Author:	Jovana Bjekić, Ph.D University of Belgrade Belgrade, SERBIA
First Author:	Andrea Antal
Order of Authors:	Andrea Antal
	Jovana Bjekić, Ph.D
	Ana Ganho-Ávila
	Ivan Alekseichuk
	Sara Asseconi
	Til Ole Bergmann
	Marom Bikson
	Jérôme Brunelin
	André Brunoni
	Leigh Charvet
	Robert Chen
	Roi Cohen Kadosh
	Lukas Diedrich
	Giordano D'Urso
	Roberta Ferrucci
	Saša R Filipović
	Paul B Fitzgerald
	Agnes Flöel
	Flavio Fröhlich
	Mark S George
	Roy H Hamilton
	Jens Haueisen
	Mark Hallett
	Christoph S Herrmann
	Friedhelm C Hummel
	Shapour Jaberzadeh
	Berthold Langguth
	Michal Lavidor

	Jean-Pascal Lefaucheur
	Carlo Miniussi
	Vera Moliadze
	Mika Nikander
	Stevan Nikolin
	Michael A Nitsche
	Alexander Opitz
	Jacinta O'Shea
	Frank Padberg
	Christian Plewnia
	Alberto Priori
	Perianen Ramasawmy
	Lais B Razza
	Simone Rossi
	John C Rothwell
	Maria A Rueger
	Giulio Ruffini
	Alexander T Sack
	Ricardo Salvador
	Klaus Schellhorn
	Teressa Schumann
	Yuichiro Shirota
	Hartwig Roman Siebner
	Axel Thielscher
	Yoshikazu Ugawa
	Susanne Uusitalo
	Anna Wexler
	Walter Paulus
	Marie-Anne Vanderhasselt
	Vincent Van Waes
	Maximilian J Wessel
	Miles Wischnewski
	Chris Baeken
	Ulf Ziemann
Abstract:	This guideline summarizes updated safety data (2017-2025) and provides expert recommendations on the use of low intensity transcranial electrical stimulation (tES) in humans. tES encompasses several techniques including transcranial direct current stimulation (tDCS), oscillatory transcranial direct current stimulation (otDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), transcranial temporal interference stimulation (tTIS), and their combinations or variations. Across over 300,000 sessions involving healthy individuals, patients with neuropsychiatric conditions, and other clinical populations, no tES-related serious adverse events (AEs) have been reported. Moderate AEs are rare and limited

to a small range of specific applications. Mild AEs are common and include transient symptoms such as localized sensations (e.g., tingling or burning), headaches, and fatigue. Similar mild AEs are also reported by individuals receiving placebo stimulation. The frequency, magnitude, and type of AEs are comparable across healthy, clinical, and vulnerable groups, including children, elderly, or pregnant women. Combined interventions (e.g., co-application with EEG, TMS, or neuroimaging) have not shown increased safety risks. Safety is well-established for both bipolar and multichannel tES when applied up to 4 mA and up to 60 min per day. Higher intensities and longer stimulation durations may also be safe, nevertheless, the number of studies using intensities above 4 mA or stimulating longer than 60 min is low. Home-based use of treatments is growing rapidly, leveraging remote supervision to provide patients with greater access and enable repeated, sustained dosing paradigms. We recommend using screening and AE questionnaires in future controlled studies, in particular when planning to extend the stimulation parameters applied. We discuss recent regulatory and ethical issues.

Highlights:

- Evidence-based safety update for low-intensity tES in humans.
- No serious adverse events casually linked to tES; only mild, transient effects reported.
- Safety is consistent across healthy, clinical, and vulnerable groups.
- Home-based and combined interventions show no added safety risks.
- We recommend clear, balanced regulation to safeguard and enable progress.

Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines (2017-2025: An Update) - endorsed by the European Society for Brain Stimulation and by the International Federation for Clinical Neurophysiology

A Antal^{*1}, J Bjekić^{*2}, A. Ganho-Ávila^{3,3a}, I Alekseichuk⁴, S Asseconi⁵, TO Bergmann^{6,6a}, M Bikson⁷, J Brunelin⁸, AR Brunoni⁹, L. Charvet¹⁰, R Chen¹¹, R. Cohen Kadosh^{12,12a}, L. Diedrich¹, G. D'Urso¹³, R. Ferrucci^{14,14a}, S.R. Filipović², PB Fitzgerald¹⁵, A Flöel¹⁶, F Fröhlich¹⁷, MS George¹⁸, RH Hamilton²⁰, J Haeisen²¹, M Hallett²², CS Herrmann²³, FC Hummel^{124,24a,24b}, S Jaberzadeh²⁵, B. Langguth²⁶, M Lavidor²⁷, JP Lefaucheur²⁸, C Miniussi⁵, V Moliadze²⁹, M Nikander³⁰, S Nikolin³¹, MA Nitsche^{32,32a,32b}, A Opitz³³, J O'Shea³⁴, F Padberg³⁵, C Plewnia³⁶, A Priori^{19,37}, P Ramasawmy¹, LB Razza³⁸, S Rossi³⁹, J Rothwell⁴⁰, MA Rueger⁴¹, G Ruffini⁴², AT Sack⁴⁵, R Salvador⁴², K Schellhorn⁴³, T Schumann⁴⁵, Y Shirota⁴⁴, HR Siebner^{46,46a,46b}, A Thielscher^{46,47}, Y Ugawa⁴⁸, S. Uusitalo⁴⁹, A Wexler⁵⁰, W Paulus⁵¹, MA Vanderhasselt⁵², V Van Waes⁵³, MJ Wessel²⁴, M Wischniewski⁵⁴, C Baeken^{*38,55,56}, U Ziemann^{*57}

* shared first and last authorships

¹*Non-Invasive Brain Stimulation Lab, Department of Neurology, University Medical Center Göttingen, Georg August University, Göttingen, Germany*

²*Human Neuroscience Group, Centre for Neuroscience and Neuromodulation, Institute for Medical Research, University of Belgrade, Serbia*

³*Faculty of Psychology and Educational Sciences, University of Coimbra, Rua do Colégio Novo, Coimbra 3000-315, Portugal*

^{3a}*Center for Research in Neuropsychology and Cognitive Behavioral Intervention, Faculty of Psychology and Educational Sciences, University of Coimbra, Rua do Colégio Novo 3000-115, Coimbra, Portugal*

⁴*Stephen M. Stahl Center for Psychiatric Neuroscience, Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA*

⁵*Center for Mind/Brain Sciences - CIMeC, University of Trento, Rovereto (TN), Italy*

⁶*Neuroimaging Center (NIC), Focus Program Translational Neuroscience (FTN), Johannes Gutenberg University Medical Center, Mainz, Germany*

^{6a}*Leibniz Institute for Resilience Research (LIR), Mainz, Germany*

⁷*Department of Biomedical Engineering, The City College of New York, New York, USA*

⁸*CH Le Vinatier; Université Claude Bernard Lyon 1, CNRS, INSERM, Centre de Recherche en Neurosciences de Lyon CRNL U1028 UMR5292, PsyR2 Team, F-69500, Bron, France*

⁹*Department of Psychiatry and Peter O'Donnell Jr. Brain Institute, UT Southwestern Medical School, Dallas (TX), USA.*

¹⁰*Department of Neurology, New York University Grossman School of Medicine, New York NY USA*

¹¹*Division of Neurology, Department of Medicine, University of Toronto and Krembil Research Institute, Toronto, Ontario, Canada*

¹²*School of Psychology, University of Surrey, Guildford, UK*

^{12a}*Cognite Neurotechnology Ltd, Oxford, UK*

¹³*Department of Psychiatry, University of Campania "Luigi Vanvitelli", Naples, Italy*

¹⁴*Department of Oncology and Emato-Oncology of University of Milan, Italy*

^{14a}*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*

¹⁵*School of Medicine and Psychology, Australian National University, Canberra, ACT, Australia*

¹⁶*Department of Neurology, University Medicine Greifswald, Greifswald, Germany; German Center for Neurodegenerative Diseases (DZNE), Standort Rostock/Greifswald, Greifswald, Germany*

¹⁷*Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

¹⁸*Brain Stimulation Division, Medical University of South Carolina, and Ralph H. Johnson Veterans Affairs Medical Center, Charleston, SC, USA*

²⁰*Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA*

²¹*Institute of Biomedical Engineering and Informatics, Technische Universität Ilmenau, Germany*

²²*Human Motor Control Section, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD, USA*

- ²³Experimental Psychology Lab, Department of Psychology, European Medical School, Carl von Ossietzky Universität, Oldenburg, Germany
- ²⁴Defitech Chair of Clinical Neuroengineering, Neuro-X Institute (INX), École Polytechnique Fédérale de Lausanne (EPFL), Geneva, Switzerland.
- ^{24a}Defitech Chair of Clinical Neuroengineering, Neuro-X Institute (INX), EPFL Valais, Clinique Romande de Réadaptation Sion, Switzerland.
- ^{24b}Clinical Neuroscience, University of Geneva Medical School, Geneva, Switzerland.
- ²⁵ Monash University, Victoria, 3199, Australia
- ²⁶Department of Psychiatry and Psychotherapy, University of Regensburg at Bezirksklinikum
- ²⁷Department of Psychology and the Gonda Brain Research Center, Bar Ilan University, Ramat Gan, Israel
- ²⁸Department of Clinical Neurophysiology, Henri Mondor Hospital, Assistance Publique – Hôpitaux de Paris, and UR 4391, Nerve Excitability and Therapeutic team (ENT), Faculty of Medicine, Paris Est Créteil University, Créteil, France
- ²⁹Institute of Medical Psychology and Medical Sociology, University Medical Center Schleswig-Holstein, Kiel University, Kiel, Germany
- ³⁰Sooma Oy, Atomitie 5C, Helsinki, Finland
- ³¹University of New South Wales, Sydney, Australia
- ³²Department of Psychology and Neurosciences, Leibniz Research Centre for Working Environment and Human Factors, Dortmund
- ^{32a}German Centre for Mental Health (DZPG), Bochum
- ^{32b}Bielefeld University, University Hospital OWL, Protestant Hospital of Bethel Foundation, University Clinic of Psychiatry and Psychotherapy
- ³³Department of Biomedical Engineering, University of Minnesota, Minneapolis, USA
- ³⁴Oxford Centre for Human Brain Activity (OHBA), Department of Psychiatry, Warneford Hospital, University of Oxford, OX3 7JX, U.K.
- ³⁵Department of Psychiatry and Psychotherapy, Munich Center for Brain Stimulation, Ludwig-Maximilian University Munich, Germany
- ³⁶Department of Psychiatry and Psychotherapy, Neurophysiology & Interventional Neuropsychiatry, University of Tübingen, Germany and German Center for Mental Health (DZPG)
- ³⁷Clinica Neurologica III, ASST Santi Paolo e Carlo di Milano, Dipartimento di Scienze della Salute, Università degli Studi di Milano, Italy
- ³⁸Ghent Experimental Psychiatry (GHEP) lab, Faculty of Medicine and Health Sciences, Department of Head and Skin, Ghent University, Ghent, Belgium
- ³⁹Department of Medicine, Surgery and Neuroscience, Human Physiology Section and Neurology and Clinical Neurophysiology Section, Brain Investigation & Neuromodulation Lab, University of Siena, Italy
- ⁴⁰UCL Institute of Neurology, London, UK
- ⁴¹University of Cologne, Faculty of Medicine and University Hospital, Department of Neurology, Cologne, Germany
- ⁴²Neuroelectrics, Av. Tibidabo 47bis 08035-Barcelona, Spain
- ⁴³neurocare group AG, Albert-Einstein-Str. 3, Ilmenau, Germany
- ⁴⁴Department of Clinical Laboratory, the University of Tokyo Hospital, Tokyo, Japan
- ⁴⁵Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, The Netherlands
- ⁴⁶Danish Research Centre for Magnetic Resonance, Department of Radiology and Nuclear Medicine, Copenhagen University Hospital Amager and Hvidovre, Hvidovre
- ^{46a}Department of Neurology, Copenhagen University Hospital Bispebjerg and Frederiksberg, Copenhagen, Denmark
- ^{46b}Institute for Clinical Medicine, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark
- ⁴⁷Department of Health Technology, Technical University of Denmark, Kongens Lyngby, Denmark
- ⁴⁸Department of Human Neurophysiology, Fukushima Medical University, Japan
- ⁴⁹Department of History, Culture and Communication Studies/ Philosophy, University of Oulu, Finland

⁵⁰*Department of Medical Ethics and Health Policy, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA*

⁵¹*Department of Neurology, Ludwig Maximilians University, Munich, Germany*

⁵²*Ghent University, Ghent, Belgium*

⁵³*Université Marie et Louis Pasteur, INSERM, UMR 1322 LINC, F-25000 Besançon, France*

⁵⁴*Department of Psychology, University of Groningen, Groningen, The Netherlands*

⁵⁵*Department of Psychiatry, University Hospital Brussel (UZ Brussel), Brussels, Belgium. Neuroprotection and Neuromodulation Research Group (NEUR), Center for Neurosciences (C4N), Vrije Universiteit Brussel (VUB), Brussels, Belgium*

⁵⁶*Department of Electrical Engineering, Eindhoven University of Technology, Eindhoven, the Netherlands*

⁵⁷*Department of Neurology & Stroke, and Hertie Institute for Clinical Brain Research, University of Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany*

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Conflicts of interest

AA is the vice president of the European Society for Brain Stimulation, Member-at-Large at the EMEAC – IFCN, she serves as a paid consultant at NeuroConn, Ilmenau, and she is a paid advisor at Electromedical Products International (Pulvinar), USA. Member of the advisory board at PlatoScience, has non-financial support from Sooma Medical™.

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FF is a paid consultant and shareholder of Electromedical Products International (EPI) and is the inventor of non-invasive brain stimulation technology for which he receives royalty payments from UNC.

HRS has received honoraria as speaker and consultant from Lundbeck AS, Denmark, and as editor (Neuroimage Clinical) from Elsevier Publishers, Amsterdam, The Netherlands. He has received royalties as book editor from Springer Publishers, Stuttgart, Germany, Oxford University Press, Oxford, UK, and from Gyldendal Publishers, Copenhagen, Denmark.

KS is an employee and shareholder of Neurocare group AG

LD has received nonfinancial support for research from NeuroCare. He has received honorarium from NeuroCare for a training course.

MAN is a member of the Scientific Advisory Boards of Neuroelectrics and Precisis.

MSG serves as a consultant to Abbott (DBS), Livanova (VNS) and Neuralief (trigeminal). He has ongoing grants from Livanova and Abbott.

In the last 3 years **PBF** has received equipment for research from Neurosoft and Nexstim. He has served on a scientific advisory board for Magstim and received speaker fees from Otsuka. He has also acted as a founder and board member for TMS Clinics Australia and Resonance Therapeutics.

PR has received nonfinancial support for research from Sooma Medical™, NeuroCare, and QuantalX Neuroscience. He has received honorarium from NeuroCare for a training course.

RCK serves on the scientific advisory boards of Neuroelectrics Inc., Innosphere Inc., is the founder and shareholder of Cognite Neurotechnology Ltd

RF and **AP** are shareholder of Newronika SpA, Italy

SA is named inventor on a patent application (WO/2022/106850) jointly submitted by the University of Birmingham (UK), and Dalhousie University (CA), titled "Improving cognitive function".

SR is member of the advisory board of Sinaptica

UZ serves on the scientific advisory board of CorTec GmbH (Freiburg, Germany).

Other authors have no conflict of interest to declare

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- We recommend clear, balanced regulation to safeguard and enable progress.

Abstract

This guideline summarizes updated safety data (2017-2025) and provides expert recommendations on the use of low intensity transcranial electrical stimulation (tES) in humans. tES encompasses several techniques including transcranial direct current stimulation (tDCS), oscillatory transcranial direct current stimulation (otDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), transcranial temporal interference stimulation (tTIS), and their combinations or variations. Across over 300,000 sessions involving healthy individuals, patients with neuropsychiatric conditions, and other clinical populations, no tES-related serious adverse events (AEs) have been reported. Moderate AEs are rare and limited to a small range of specific applications. Mild AEs are common and include transient symptoms such as localized sensations (e.g., tingling or burning), headaches, and fatigue. Similar mild AEs are also reported by individuals receiving placebo stimulation. The frequency, magnitude, and type of AEs are comparable across healthy, clinical, and vulnerable groups, including children, elderly, or pregnant women. Combined interventions (e.g., co-application with EEG, TMS, or neuroimaging) have not shown increased safety risks. Safety is well-established for both bipolar and multichannel tES when applied up to 4 mA and up to 60 min per day. Higher intensities and longer stimulation durations may also be safe, nevertheless, the number of studies using intensities above 4 mA or stimulating longer than 60 min is low. Home-based use of treatments is growing rapidly, leveraging remote supervision to provide patients with greater access and enable repeated, sustained dosing paradigms. We recommend using screening and AE questionnaires in future controlled studies, in particular when planning to extend the stimulation parameters applied. We discuss recent regulatory and ethical issues.

Keywords: tDCS, tACS, tES, safety, adverse events, ethics, regulation, training

List of Abbreviations

AC	alternating current
AD	Alzheimer's Disease
AE	adverse event
ALS	amyotrophic lateral sclerosis
ANS	autonomic nervous system
CES	cranial electrical stimulation
CNS	central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
DBS	deep brain stimulation
DC	direct current
DLPFC	dorsolateral prefrontal cortex
ECT	electroconvulsive therapy
EEG / sEEG	electroencephalography / stereo EEG
EF	electric field
ESBS	European Society for Brain Stimulation
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFCN	International Federation of Clinical Neurophysiology
IRB	institutional review board
LOTES	limited-output tES
MCI	mild cognitive impairment
MDD	major depressive disorder
MDR	Medical Device Regulation
MEG	magnetoencephalography
MR / MRI / fMRI	magnetic resonance / MR imaging / functional MRI
MS	multiple sclerosis
NIBS	noninvasive brain stimulation
OCD	obsessive compulsive disorder
otDCS	oscillatory transcranial direct current stimulation
ONS	optic nerve stimulation
PD	Parkinsons disease
PFC	prefrontal cortex
PMDA	Pharmaceuticals and Medical Devices Agency
PTSD	posttraumatic stress disorder
RCT	randomized control trial
RS-tES /RS-tDCS	remotely supervised tES/tDCS
rtACS	repetitive transorbital alternating current stimulation
SAE	serious adverse event
SE	side effect
SSRI	selective serotonin reuptake inhibitors
TBS	theta burst stimulation
tACS	transcranial alternating current stimulation
tDCS	transcranial direct current stimulation
tES	transcranial electrical stimulation
tsDCS	transcutaneous spinal direct current stimulation
tTIS	transcranial temporal interference stimulation
tRNS	transcranial random noise stimulation
TMS /rTMS	transcranial magnetic stimulation / repetitive TMS
	visual-analogue scale

1. Introduction

1.1. Overview of the update

Low intensity transcranial electrical stimulation (tES) encompasses a group of non-invasive brain stimulation techniques—including transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS)—that apply low intensity electrical currents to the scalp to modulate cortical excitability and neural oscillations. The applications of tES have grown exponentially since its development in the early 2000s. The safety, ethical, legal, regulatory and application guidelines published in 2017 (Antal et al., 2017a) provide a comprehensive overview of the state of the art including the available data up to 2016. With the field rapidly progressing, we provide here an update of the safety, regulatory, and application guidelines based on the available evidence published until the middle of 2025. The essentials of the present manuscript were agreed upon at a two-day conference held in Munich, Germany on 12th and 13th June 2025. Participants included research and clinical experts from neurophysiology, neurology, cognitive neuroscience, and psychiatry, as well as ethicists. Industry representatives (i.e., tES equipment manufacturers) also contributed to safety and regulatory issues.

To ensure a comprehensive update, we conducted a systematic search of the literature: the PubMed database using a combination of tES and safety-related keywords (see Appendix for search syntax and output) published between 01/01/2017 and 31/12/2024. The search identified 937 records, which were narrowed down to 340 records after screening titles and abstracts. The records were then categorized based on their type (case reports, qualitative reviews, systematic reviews, meta-analyses, randomized controlled trials, guidelines, and opinion articles) and the topics they addressed (healthy participants, neurology, psychiatry, cognition, pediatrics, elderly populations, pregnancy, ethics, animal studies, modeling and theoretical works, accelerated protocols, and home-based stimulation). Each category was reviewed by experts in the respective research areas, who were encouraged to ensure the inclusion of all relevant works by conducting additional topic-focused searches in different databases (e.g., see the section on aging population), as well as to include any gray-literature sources, and then provided a narrative summary of the relevant findings.

We relied on summarizing and interpreting data regarding (1) available animal studies, (2) computational modeling, and (3) human trials, including reports on healthy participants, patients, and vulnerable groups, such as children, elderly, and pregnant women. With regard to animal data, the main effort was devoted to understanding the translation of findings to human applications (e.g., the relationship of dose of the stimulation and safety).

Special stimulation conditions that are increasingly used during the last years, e.g., combination of tES with other methods, such as pharmacological and non-pharmacological treatments, stimulating patients with intracranial implants, combination of tES with transcranial magnetic stimulation (TMS) or functional magnetic resonance imaging (fMRI), and EEG were also considered, to assess if they change the risk-profile of the tES application. Furthermore, other stimulation protocols, such as temporal interference stimulation - tTIS and transorbital stimulation) and other settings than ‘transcranial’, in which recent safety data are available, were also integrated (e.g., transcutaneous spinal direct current stimulation (tsDCS)).

In this paper, we first provide an overview of the terminology of side effects (SE) and adverse events (AE), technical parameters and basic principles of low intensity tES used alone or combined with other methods, and safety aspects of the stimulation with a summary of the published AEs in healthy participants and different patient populations. The presumed mechanisms and the efficacy of tES in eliciting desired outcomes are not within the scope of this review except for instances, in which they inform about safety. Other stimulation methods such as cranial electrical stimulation (CES) or electroconvulsive therapy (ECT) are also not incorporated here. We also present recent regulatory issues across continents and recommend standards for reporting in research and clinical practice, and finally we summarize existing data and provide recommendations for training and certification and future safety monitoring.

Consensus with regard to the definitions, recommendations, among others were reached after extensive discussions and by voting. The experts first summarized safety data related to their fields and answered questions in several rounds. The key results were presented and discussed at the meeting in Munich. After that the experts were encouraged to support or revise their earlier answers in light of the replies and critique of other members of the panel. The meeting was organized by the Brain Stimulation Special Interest Group of the International Federation of Clinical Neurophysiology (IFCN) and the European Society for Brain Stimulation (ESBS). The ESBS and IFCN have endorsed the guideline.

1.2. Basic aspects: Nomenclature and explanations

This document adopts the definitions used in the previous edition of this guideline (Antal et al., 2017a) which align with earlier proposals (e.g., (Bikson et al., 2016; Woods et al., 2016), and the nomenclature consensus (Bikson et al., 2019). Additional key terms are clarified below.

Low intensity tES is defined as electric current stimulation with total intensities of ≤ 4 mA (for AC waveforms ≤ 4 mA peak-to-peak), a total stimulation duration of up to 60 min per day, and using electrode sizes between 1 cm² and 100 cm² with frequencies between 0 and 10,000 Hz. For multi-channel stimulation the total intensity is the sum across all electrodes of the same polarity. For multiple sessions per day the total duration is the sum of all session durations. The current can be of constant intensity and polarity (tDCS) or can be of variable intensities, polarities, or both, alternating between polarities (either at a steady sinusoidal frequency, as in tACS, or a randomly changing frequency, as in tRNS) or within the same polarity (as in oscillatory tDCS (otDCS)) (Guleyupoglu et al., 2013). The intensity of tDCS is always defined as baseline-to-peak, while with tACS and tRNS baseline-to-peak or peak-to-peak intensities can be used and should be explicitly specified. The 4 mA and 60 min parameter limits are based on convention (both for 'low' and 'limited'; (Antal et al., 2017a; Bikson et al., 2016, 2018, 2019, 2023) and do not represent formal safety limits. Throughout this review, statements are specific to low intensity tES (as herewith defined) unless otherwise indicated, and studies with evidence for safety which exceed 4 mA or 60 min total per day are also described. The use of intensity ramp-ups and ramp-downs is universal in tES studies and so the claims made in this report (e.g., regarding tolerability) imply the use of ramp up/down. Generally, the ramp up/down durations are 30-60 s and are not calculated in the stimulation duration (Bikson et al., 2019). Sham typically includes brief ramp-up and ramp-down phases, one at the onset and one at the end of the stimulation session, each lasting no more than one minute in total.

Safety is best considered under medical device and drug regulations, which generally define a procedure as safe if the expected benefits outweigh potential risks. An intervention or procedure, such as tES is considered safe if it does not pose an unreasonable risk when implemented as intended, according to defined procedures and administered by trained personnel, and when its benefits justify any known, expected or remaining risks. According to the EU-MDR, safety is determined through a benefit–risk analysis (Article 2), and risks must be mitigated as far as possible, in line with current technology and knowledge.

The term **side effect (SE)** implies a known causal relationship with the intervention and refers to an effect different from the targeted or intended one. An SE is not always harmful or unpleasant, it may also be neutral or even beneficial. Following the recommendations of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH; www.ich.org) (Baber, 1994; ICH Expert Working Group, 1994) and the Common Terminology Criteria for Adverse Events (CTCAE) v5 (U.S. Department of Health and Human Services, 2017), the term SE will be used in this document when necessary for historical or other legitimate reasons (e.g., communications with participants/patients, or discussions on physiological mechanisms).

Instead, we follow ICH and CTCAE guidelines and use the term **adverse event (AE)**, defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the procedure, regardless of proven causality. AEs are graded according to severity: Grade 1 are mild AEs, defined as involving mild symptoms for which no medical treatment is necessary (e.g., skin redness or tingling during tDCS). Grade 2 are moderate AEs with the need of local or noninvasive treatment (e.g., in the case of tES, the local application of a skin cream for a skin irritation). Serious AEs (SAE) (Grade 3) are severe or medically significant but not immediately life-threatening events, which include the requirement for

inpatient hospitalisation or prolongation of hospitalisation. Grade 4 includes life-threatening AEs, where urgent intervention is often required, while Grade 5 means death related to AE. An AE is generally considered unexpected if it is not listed in the information brochure or is not listed at the specificity or severity level that has been observed, or it is not consistent with the risk information described in the investigational plan (FDA regulations, 21CFR312.32, safety reporting).

Following the ISO 14155:2020 classification and CTCAE grading, all unintended effects fall in one of two categories: (1) **Non-serious AEs:** Grade 1–2: benign, short-lasting effects that may affect comfort or perceived burden, but posing no safety risk. These correspond to commonly reported SEs (for details see Section 6) (2) **Serious AEs:** Grade 3–5: events of safety concern, such as those requiring hospitalization or causing lasting harm. Therefore, for safety considerations, only serious AEs are directly relevant, while non-serious AEs and known SE of tES are more appropriately evaluated in terms of tolerability and participant burden.

1.3. History of tES and state of the art

The origins of tES can be traced back to electrotherapy practices in the 18th and 19th centuries, when rudimentary electrical devices were used to relieve melancholia (Aldini, 1804), headaches, and induce electronarcosis and electrosleep (d'Arsonval, 1892; Leduc, 1902; Robinovitch, 1906). However, their effectiveness and mechanisms of action were largely inconclusive, and not extensively explored (Lolas, 1977). Scientific foundations for modern tES applications were laid much later in the 20th century, through early experimental studies in humans and animal models on cerebral excitability, activity, and neuroplasticity (Guleyupoglu et al., 2013). Modern applications of tES began to gain momentum in the early 2000s, when systematic investigations demonstrated that tDCS could induce polarity-dependent changes in cortical excitability in a safe and reproducible manner (Nitsche & Paulus, 2000; Priori et al., 1998), catalyzing a new wave of cognitive and clinical neuroscience research. What followed was a rapid diversification of techniques. The stimulation targets expanded to also include the cerebellum and spinal cord (Priori et al., 2014). Oscillatory stimulation protocols, such as tACS and tRNS, offered a unique approach to interacting with brain networks (Antal et al., 2007, 2017a). tACS in particular introduced the ability to interact with endogenous neural oscillations, thus offering a tool for modulation and investigation of specific brain rhythms underpinning cognition and behavior (Wischniewski et al., 2023). These developments prompted a growing interest in network-based, state-dependent, and frequency-specific stimulation paradigms tailored to a specific clinical population, brain mechanism, or personal brain dynamics.

The simplicity, portability, and low cost of tES devices, combined with their favorable safety profile, have contributed to widespread adoption in both basic and clinical neuroscience research. In recent years, the field has expanded significantly, with tES being investigated across a variety of applications including neurorehabilitation, psychiatry, aging, epilepsy, and cognitive enhancement. One direction of progress toward clinical application is the emergence of multi-session and multi-day trials (Couture et al., 2025; Schwippel et al., 2024). This progress has been accompanied by increased focus on improving the spatial, functional, and temporal precision of tES. Specifically, introducing individualized stimulation protocols improves functional precision of the intervention. Such protocols leverage computational modeling for tailored stimulation dose (Puonti, Van Leemput, et al., 2020), optimized electrode locations adapted to individual anatomy (Ruffini et al., 2014), physiology-inspired stimulation frequencies, polarities, and waveforms (Zaehle et al., 2011), and connectivity inspired manipulation with phases of periodic currents (Alekseichuk et al., 2019). Multimodal integration with EEG and neuroimaging enables individual targeting based on structural and functional idiosyncrasies and closed-loop designs, which promise more robust effects. Additionally, large-scale computational models have promoted our understanding of current distribution and prompted new approaches to precision and network targeting. Modeling was initially used for post hoc explanations of observed study results and has subsequently been increasingly exploited for ad-hoc planning tools and meta-analytic frameworks. The second notable source of modern understanding of tES mechanisms comes from translational animal research (Johnson et al., 2019; Krause et al., 2019; Vöröslakos et al., 2018), improving the comprehension of dosing and brain state selectivity. However, the rapid adoption of tES has outpaced the development of unified methodological, ethical, legal, and regulatory standards. As the field evolves, it becomes increasingly

important to reassess safety guidelines, ethical considerations and regulatory frameworks especially in light of emerging use in vulnerable populations, home-based applications, expanded clinical indications, and multimodal approaches.

2. Principle-based verification of tES

2.1. Mechanism of action - neuronal polarization and other mechanisms

The low intensity tES modulates brain activity primarily through subthreshold neuronal polarization. tES induces electric fields that shift the membrane potentials without directly causing action potentials, making neurons more or less likely to fire in response to ongoing synaptic input. Such modulation can influence synaptic efficacy, alter neuronal excitability, and shape network-level oscillatory dynamics. The mechanisms of low-intensity tES vary, depending on the current properties and electrode placement. For instance, tDCS which always has at least one anode and at least one cathode, is explained by a sustained polarity-specificity change in membrane potential (Buch et al., 2017; Jackson et al., 2017). Direct effects of tES that follow neuronal polarization by tES-generated brain EFs have been extensively studied (Bikson et al., 2010; Froehlich & McCormick, 2010; A. Liu et al., 2018). tACS applies sinusoidal current through two or more electrodes, thus there is no fixed anode or cathode given the oscillatory nature of the current, and the proposed mechanism action is linked to modulation of brain oscillations (W. A. Huang et al., 2021; Reato et al., 2013).

Still, there are additional parallel supplementary mechanisms to be considered. As summarized previously (Antal et al., 2017a), these include galvanotaxis and electroporation - both requiring higher intensities than those applied in tES. Furthermore, the effects of tES on glial cells have been demonstrated in animal studies, including implications for tDCS (Cancel et al., 2022; Monai et al., 2016; Ruohonen & Karhu, 2012; Tsui et al., 2022). Next, effects of tES, especially tDCS, on brain clearance mechanisms (Khadka et al., 2023; Y. Wang & Monai, 2024; Xia et al., 2020), as well as on vascular and metabolic function (Bahr-Hosseini & Bikson, 2021; Gellner et al., 2023; Khadka et al., 2018; Y. Luo et al., 2022; Sprugnoli et al., 2019) have also been documented, including changes in blood brain barrier/endothelial cell activation (Cancel et al., 2018; Xia et al., 2021). These mechanisms are not independent of each other or of direct neuronal stimulation (e.g. stimulation of the blood brain barrier will impact both neurons and glia, leading to brain transport/clearance changes, and so impacting neuronal function/metabolism). It remains important to understand if/how a given form of tES activates one of these parallel pathways as this may indicate unique therapeutic mechanistic pathways, as well as better explain secondary (following) neuronal changes.

Depending on dose, tES may also induce or attenuate neuroinflammatory processes in the brain. In rodents, anodal tDCS ($\sim 100 \text{ kC/m}^2$) decreases the number of activated microglia (Pikhovych et al., 2016), while higher charge densities have pro-inflammatory effects (Rueger et al., 2012). Effects vary by species, disease model, timing, and stimulation parameters. For example, anodal tDCS (4 kC/m^2) downregulates hippocampal inflammatory mediators in a chronic pain model (Spezia Adachi et al., 2012), but upregulates them by both cathodal and anodal tDCS of the same charge density in cortical tissue in a rat epilepsy model (Regner et al., 2020). In post-stroke rodent model, cathodal tDCS ($\sim 66 \text{ kC/m}^2$) reduces microglial activation and immune cell invasion (Peruzzotti-Jametti et al., 2013) and induces a shift in microglia polarization (Braun et al., 2016), while dual-tDCS down-regulates inflammatory mediators in cortex and hippocampus (Huang et al., 2025). In contrast, anodal tDCS ($\sim 57 \text{ kC/m}^2$) applied in the acute phase of stroke increases microglia activity throughout the rat brain (Fritsch et al., 2024). In animal models of multiple sclerosis (MS) it was shown that cathodal tDCS attenuates inflammation and axonal loss (Marena et al., 2022) and that anodal tDCS enhances remyelination and reduces microglial activity (Rossi et al., 2024).

Conclusions: Neuronal function is directly modulated by low-intensity tES through membrane polarization. There remains the possibility of parallel mechanisms of action such as glia, vascular, or brain clearance stimulation. While effects can be demonstrated in isolated tissue models, it is difficult to isolate direct vs indirect effects precisely in vivo because neuronal, glial, vascular, and transport factors are tightly linked. Beyond direct neuronal effects, tES has been shown to modulate neuroinflammatory processes in a context-dependent manner—either attenuating or exacerbating inflammation depending on dose, timing, and disease model. Given the importance of these mechanisms in the etiology and the

treatment of various brain disorders, the secondary effects of tES are an important consideration, but they do not raise specific safety concerns in respect to existing practices.

2.2. Assumptions regarding dose-response relationship

tES dose is defined by all of the parameters of the stimulation device that affect the generated electric field (EF) in the body with units of V/m (or, equivalently, mV/mm) (Peterchev et al., 2012). This includes the relevant parameters of the electrode montage (skin contact area), and the intensity, waveform, polarity (if asymmetric), and the duration the current is applied for. For all waveforms except DC this includes stimulation frequency. Electrode size (area, shape) refers to the interface between the electrolyte (e.g. gel, saline) and the skin - that is specifically the surface when current flows in/out the body. Electrode current density is the current amplitude divided by the electrode size. Note this is distinct from current density in the body / brain. Electrode charge density is the total charge applied during a session divided by the electrode size. For tDCS, electrode charge density is the current density times the session duration. As with current density, care should be taken in distinguishing electrode charge density and charge densities in the body / brain. Electrode current / charge density are metrics that can be uniquely calculated given dose parameters, while the converse is not true (e.g. given only a current density one cannot calculate a unique current or electrode size).

These “extrinsic” parameters delivered by the stimulation equipment are well defined and reproducible, while factors influencing current flow patterns and physiological responses are not controllable (e.g., individual tissue properties and anatomy, age, gender, baseline neurotransmitter concentrations, genetics, dynamic state of the brain before and during stimulation). These “intrinsic” parameters shape the physiological responses to the stimulation and should therefore be considered along with the dose selection (Bikson, Name, et al., 2013; L. M. Li et al., 2019; Wei et al., 2024). This presents a challenge to researchers and clinicians when finding the ‘optimal’ dose for a given application. At present, in most studies, the dose (including all parameters: intensity, waveform, electrode size, stimulation duration) is chosen based on previously published data, prior research and clinical experience, individual measures like thresholds, computational models, summary metrics such as the electrode charge density calculated from electrode area, current, and time and related safety considerations based on human and animal experimental data.

tES produces an EF in the brain, which then governs all physiological effects. However, the relation between EF and outcome, including its accumulation over time, is not trivial and may be non-linear (Esmailpour et al., 2018; Miranda et al., 2009; Ruffini et al., 2014, p. 20). On the other hand, even though tDCS induces significant polarization changes, there is a rapid physiological “accommodation” of the axonal membrane potential to a prolonged depolarizing or hyperpolarizing current, mainly involving potassium channels, and probably limiting these changes. (Lefaucheur and Wendling, 2019). Thus, given the differences in the biophysical mechanisms of varied tES strategies, dose-response estimates are not directly comparable between methods and the only major factor controlling stimulation efficacy. Actually, optimal dosing depends on the intended neuromodulatory effects. .

With regards to informing safety standards based on animal models where brain injury was assessed, it is generally assumed that there is a monotonic dose response (i.e. risk increases with intensity). Factors for interpretation are considered below but we start by noting there is no evidence for brain injury from low intensity tES (tDCS) in humans (Bikson et al., 2016; Nitsche et al., 2004).

Skin effects depend heavily on electrode design (see Electrode section) and best practices (Khadka et al., 2018; Pilloni et al., 2022). Skin is exposed to electrode electrochemical products (Minhas et al., 2010) and higher current density than the brain (Bikson et al., 2018). Standards for skin tolerance should be developed separately and validated in human subjects through empirical testing (Minhas et al., 2010; Woods et al., 2016).

For safety, one approach to dose-response is to 1) adopt the lowest reported brain injury threshold across all animal studies and 2) rely on *electrode* current density in the animal models as an upper limit for *brain* current density in human standards. This: a) avoids assumptions about dose-response curves (Bikson et al., 2016); b) neglects variable results (Zhang et al., 2019); including c) methodological issues (e.g. electrode materials that exaggerate sensitivity in some animal studies. This is thus an overall conservative approach. Note limits developed according to this approach for brain current density do

not apply for electrode current density limits. Studies using invasive electrodes (Bikson et al., 2017) are excluded due to different injury mechanisms.

The lowest threshold needed to cause a lesion from either anodal or cathodal tDCS in rodent models can be used. Rodent data suggests higher sensitivity under anodal stimulation (Jackson et al., 2017), though studies indicate cathodal stimulation lesion threshold may be higher than previously reported (Zhang et al., 2019). Reported brain histological tissue damage thresholds for tDCS in animal models were 142.9 A/m² (Liebetanz et al., 2009), and 20 A/m² for tDCS (Jackson et al., 2017). A 20 A/m² threshold is still 10-fold higher than typical brain current density in humans (Jackson et al., 2017).

Current flow models of tDCS in humans predict the ratio of electrode/skin to brain current density greater than 10:1, and in cases greater than 100:1 (Bikson et al., 2018). In rodent models because of the lower volume (~1000x) and electrode-to-brain distance, as well as use of epicranial electrodes (which prevents skin shunting) the ratio of electrode to brain current density is lower than in humans. To relate safety threshold from rodent studies to human, translation computational models are used (Bikson et al., 2016) and would be montage specific (See modeling section).

The tDCS safety threshold for any montage/subject can be set using two factors. 1) The lowest reported current density causing brain injury in rodents: 20 A/m² (Jackson et al., 2017). Noting the majority of animal trials indicate even higher electrode current densities are safe (Blaschke et al., 2023; Braun et al., 2016; Callai et al., 2022; Fritsch et al., 2024; Milighetti et al., 2020; Sánchez-León et al., 2021; K. Zhang et al., 2019). 2) The classical “zero lesion size” threshold 5,240 mC/cm² (Liebetanz et al., 2009), which is widely referenced (Antal et al., 2017a; Liebetanz et al., 2009) and is lower than observed injury thresholds (Fritsch et al., 2024; Jackson et al., 2017; K. Zhang et al., 2019).

Conclusion and recommendations: Defining precise dose-response relationships in tES remains a significant challenge, given the complex interplay between standardized extrinsic stimulation parameters and individual-specific intrinsic factors such as anatomy, physiology, and baseline brain state. Although safety thresholds derived from animal studies serve as valuable benchmarks, their translation to humans must be approached with rigor, due to interspecies variability and methodological heterogeneity. In this context, we propose a precautionary strategy whereby 1) the lowest *electrode* current density / electrode charge density shown to be injurious in any rodent model is determined; 2) these limits are applied to set the maximum *brain* current density / brain charge density in human trials; 3) the *electrode* current density / electrode charge density limits for human trials are then derived, which may be electrode montage specific (e.g. using computational models). Low intensity tES results in brain current/charge-density well below animal safety thresholds.

2.3. Modeling (heating, induced voltages)

Computational modeling in tES provides a subject-specific estimation of current flow distribution within the head by integrating anatomical imaging (typically magnetic resonance imaging (MRI)) data with finite element models (Figure 1). These simulations allow investigation of the spatial distribution and intensity of the electric field (EF) induced by surface-applied currents (i.e., tDCS, tACS), providing information into the physical dose received by neurons in different cortical and subcortical regions. The EF magnitude and direction is the cardinal agent of tES techniques (Galan-Gadea et al., 2023; Radman et al., 2009) and it is molded by the details of individual anatomy (Mosayebi-Samani et al., 2021; Opitz et al., 2015), complex arrangement of cortical folding, and by the electrode montage (electrode positions, currents, and their geometry and composition (Miranda et al., 2013; Saturnino et al., 2015)). While the total applied current at the scalp is typically fixed across study participants (e.g., 1-4 mA), the resulting intracerebral EF can vary substantially between groups and individuals (Laakso et al., 2015), potentially contributing to variability in stimulation outcomes. Computational models are needed precisely because the relation between dose and brain EF is complex (i.e it cannot be predicted by rules of thumb).

Therefore, a primary function of computational models is to guide the development of new electrode montages and dosing strategies for targeting specific brain regions (Dmochowski et al., 2011; Ruffini et al., 2014; Saturnino et al., 2019), as well as to characterize which regions are affected by existing configurations (Splittgerber, Salvador, et al., 2020). Accordingly, one of the most common uses of computational modeling is the comparison of different montages in terms of their capacity to target desired brain areas.

In this context, computational modeling is a valuable tool for investigating EF distributions across diverse anatomical profiles, including pediatric populations and individuals with neurological conditions (Kasten et al., 2019; Laakso et al., 2019; Van Hoornweder et al., 2022). For example, children, who typically have thinner skulls, may experience significantly stronger cortical EF compared to adults (Ciechanski et al., 2018; Schaper et al., 2023). Individualized EF distributions can also be estimated in the presence of anatomical abnormalities, such as skull defects (Opitz et al., 2018), as well as in stroke patients with lesions filled with cerebrospinal fluid (Minjoli et al., 2017; Yoon et al., 2024) and patients with implants (Mercadal et al., 2022). In such cases, simulations can identify localized field enhancements in the brain or surrounding tissues, including the scalp - an important consideration for safety and risk assessment. The precision of these predictions, however, depends on the accuracy of the model, not necessarily the complexity (Bikson & Datta, 2012). Since the introduction of MRI-derived models (Datta, Bansal, et al., 2009), it has been recognized that the CSF compartment should be segmented to avoid direct brain-skull contact and that cortical gyration may generate hotspots (i.e., strong EFs) between, rather than directly beneath, electrodes.

Typical models include six tissue compartments: scalp, skull, CSF, grey matter, white matter, and air (Guidetti et al., 2022). However, these compartments encompass multiple tissue types, and assumptions must be made either through explicit compartmentalization or by assigning aggregate conductivities. For instance, the space between brain and skull is not pure CSF but includes meninges; using a reduced conductivity of 0.8 S/m instead of 1.65 S/m for this compartment has been proposed for greater accuracy (Jiang et al., 2020; Weise et al., 2022). Similarly, the scalp is typically modeled as a single compartment, with an aggregate conductivity of 0.2-0.465 S/m, even though it includes layers such as fat. Such simplifications are often necessary but introduce potential sources of deviation from real-world outcomes.

While invasive measurements in patients have addressed model accuracy (Guidetti et al., 2022; Y. Huang et al., 2017; Opitz et al., 2016; Puonti, Saturnino, et al., 2020), discrepancies remain, especially at the individual level. Key challenges include uncertainties in tissue resistivity and permittivity, particularly at low frequencies (Saturnino et al., 2019), as well as poorly understood conductivity profiles of pathological and perilesional tissues (Datta et al., 2010; Sprugnoli et al., 2019). Precise segmentation of lesions may require multimodal imaging beyond standard T1-weighted MRI. Similarly, a consensus has yet to be reached on the best way to model implants, such as titanium plates and SEEG leads (Alonso et al., 2023; Karimi et al., 2025; Mercadal et al., 2022). Some evidence suggests metals may behave as non-conductors at low frequencies due to insulating tissue-metal interfaces (Mercadal et al., 2022).

Underlying these modeling efforts is a key conceptual simplification: the assumption that the EF in a region of interest predicts the degree of modulation. This is known as the quasi-uniform assumption (Bikson, Dmochowski, et al., 2013), which posits that at the scale of individual neurons, the EF can be treated as spatially uniform. The effects of (uniform) EFs on neuronal polarization depend strongly on both the magnitude and direction of the EF relative to a neuron's morphology and orientation (Bikson et al., 2004). Therefore, modeling the EF vector, not just its magnitude, is critical (Galan-Gadea et al., 2023). This assumption remains implicit in most large-scale tES simulations, including when modeling effects on neurons (Aberra et al., 2023; Rathour & Kaphzan, 2024) or other cell types (Khadka & Bikson, 2022), where each cell is treated as being exposed to a locally uniform field.

The EF strength and its spatial distribution in tACS are expected to be similar to that observed with tDCS (Y. Huang et al., 2017; Opitz et al., 2016). It remains unclear whether the high electric permittivity of brain tissues can significantly affect the strength of the EF in the brain and shift the phase of the sinusoidal waves, in particular with higher frequencies (Gaugain et al., 2023).

Models focused on skin current flow have informed electrode design, as tolerability of tES is often related to skin effects (Khadka et al., 2018; Kronberg & Bikson, 2012; Saturnino et al., 2015). The skin is, in fact, a complex multilayer/structures barrier, and efforts have been made to model current flow through these structures explicitly (Gomez-Tames et al., 2016; Khadka & Bikson, 2020). Practical factors affecting tolerability (such as electrodes drying or leaking saline/gel) may not be addressed by idealized computational models.

Notwithstanding the noted limitations, EF simulations can support risk analyses. For example, it is reasonable to assume that AE scales with the local electric field strength. When simulations predict EF levels within previously validated safety margins, this supports confidence in a given approach.

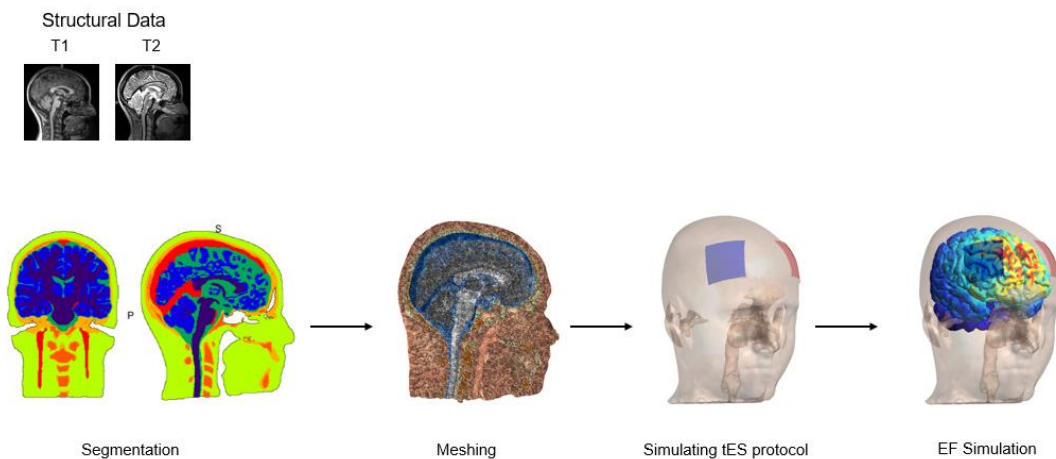
Extending simulations beyond the EF to include tissue heating can help to improve their utility for risk assessment. Heating of the brain during tES, scales with the strength and duration of the electric field, and can be predicted by bioheat models. For conventional tES protocols predicted heating is insignificant (not hazardous) (Datta, Elwassif, et al., 2009) including in the presence of implants, (Karimi et al., 2025), but might be re-evaluated for higher doses, atypical anatomy, or specific implants. Heating simulations at the MRI radiofrequency, complemented by measurements of skin temperature increases, have been important for the safety evaluation of tES electrodes and cables used during magnetic resonance scanning (Gregersen et al., 2021).

Models of other mechanisms of AEs, such as electrochemical reactions at the skin-electrode interface, are not well established, limiting the possibilities offered by simulations for risk assessments of those aspects. Computational models are also a key tool in scaling rodent to human dosimetry and developing safety standards (Bikson et al., 2016).

Previous findings on anatomical differences in head and cortical bone structure between males and females (Russell et al., 2014), suggest that females tend to have thicker cranial bone structures, which may reduce the intensity of electrical currents reaching brain tissue. However, such differences may be less impactful than general anatomical (size) differences across individuals. These findings along with the reciprocal dynamics between fluctuating sex and reproductive hormones and cortical excitability (Finocchi & Ferrari, 2011; Aftanas et al., 2022), remain underexplored.

Conclusions and recommendations: Models are an important part of risk analyses, especially in relating dose to EF and for identifying possible worst-case scenarios. No significant / hazardous brain heating is predicted during conventional protocols. However, given the model uncertainties, the need for further validation, and the incomplete understanding of the link between EF and AEs, it is recommended that EF modeling not be used on its own to assess safety. Instead, it should be complemented by empirical safety data and established risk assessment procedures.

Figure 1. Electric field modeling pipeline.



3. Electrode design for tES

Electrode design and placement govern brain current flow and thus, the spatial effects of stimulation (for a detailed review, see (Solomons & Shanmugasundaram, 2020)). While the shape and materials of the electrode have moderate influence on brain current flow, the primary importance of electrode design is tolerable effects on the skin. We summarize electrode design impact on brain current flow and on skin effects.

Conventional tDCS uses two “pad” electrodes (one anode, one cathode) of comparable size (25-35 cm²). The term “return” electrodes does not mean an electrode is inert but rather reflects the hypothesis that it plays a less critical role in the targeted outcome. Notably, the return electrode can be either the anode

or cathode, depending on the montage and the intended direction of current flow. Similarly, designations like “anodal tDCS” or “cathodal tDCS” highlight the presumed functional importance of the anode or cathode, respectively, within a given protocol (Bikson et al., 2019). Increasing the size of one electrode relative to the other has been proposed as a method to reduce the impact of the larger electrodes (Nitsche et al., 2007), though computational models suggest this has moderate effect (Bikson et al., 2010). Positioning the “return” electrode in an extracephalic position does not make it inert but produces current through the deep brain (Noetscher et al., 2014; Sadeghihassanabadi et al., 2022).

Scalp electrodes used for HD-tDCS® are smaller (~2.5 cm²) (Minhas et al., 2010). The use of smaller electrodes in itself provides only a moderate benefit in focality (Miranda et al., 2009). However, multiple HD electrodes can be arranged that can alter current flow. In the 4x1 Laplacian montage (Datta, Bansal, et al., 2009), the center electrode determines the active polarity and the radius of the four electrode ring controls focality (Alam et al., 2016). Overall, the 4x1 montage enables a more focal cortical current flow (Edwards et al., 2013). It has been applied to multiple cortical targets including the motor cortex and the DLPFC (Cacciamani et al., 2024; Caparelli-Daquer et al., 2012; Hemmerich et al., 2024; Johari et al., 2022; Kuo et al., 2013; Müller et al., 2022). The 4x1 montage was also used to deliver tACS (Gebodh et al., 2024; Grover et al., 2022; D.-W. Zhang et al., 2022) or otDCS (Manojlović et al., 2025).

Alternatively, multiple electrodes distributed across several sites can be used to optimize the EF strength in the target brain region or to deliver network-targeted stimulation (Fisher et al., 2017; Gregoret et al., 2023). Another approach using four electrodes, tTIS, was recently shown to be well tolerated (Cassarà et al., 2025; Vassiliadis et al., 2024). There is a tradeoff between maximum EF intensity in the brain and focality (Alam et al., 2016). With multi electrode montages, it is also possible to provide higher total current by splitting current to individual electrodes (Harrie et al., 2023).

Electrode design plays a fundamental role in tolerability. While for any given current, decreasing electrode size will proportionally increase current density; electrode materials have a more important role in tolerability. For example, well-designed HD electrodes produce higher current density than conventional tDCS pad electrodes without necessarily enhancing skin sensation (Reckow et al., 2018; Turski et al., 2017). Electrode shape appears to have minimal effect on the resulting sensation (Ambrus et al., 2011; Minhas et al., 2011). The resistivity of the electrolyte (sponge or hydrogel) may impact tolerability (Dundas et al., 2007; Khadka et al., 2018). Skin lesions are not an expected AE of tES when the best practices are followed and appropriate equipment used; essentially every case-report of a skin lesion during tDCS was correlated to poor technique or technology (Pilloni et al., 2021). Impedance measurements are a valued quality-control step to identify potentially non-ideal electrode set-up (e.g. electrolyte dries up). However, low impedance is neither a necessary or sufficient condition to ensure tolerated and reliable stimulation. It is possible for an approach to show low impedance but not be tolerated (Woods et al., 2016). For home-based techniques (see Section 10.4), and use in the MRI (see Section 9.1.), special considerations apply.

Finally, given the central role of electrode design in sensation, it is also a relevant factor in the blinding reliability (e.g. electrode designs that produce less sensation in the active arm will produce more effective blinding). This is an important point when considering the reliability of sham across studies that may not use the same electrode designs.

Conclusions and recommendations: A multitude of possible electrode shapes, materials, and placements are possible. Electrode montage primarily shapes current flow through the brain while electrode design primarily impacts tolerability. Skin preparation (cleaning and drying) is recommended, while abrasion is not valued or recommended. Skin lesions are not an expected AE of tES using verified devices/electrodes and standard protocols (e.g. over intact skin). Electrodes verified for specific tES dose should be used; electrodes not designed for stimulation (recording electrodes) or for distinct stimulation applications (eg. TENS electrodes) are not a priori verified for tES. For sponge electrodes, using desalinated (tap) water is not recommended. Appropriate protocols for electrode preparation and placement are required. Protocols for electrode re-use or single-use should be guided by the manufacturer’s recommendations. Tolerability is always a function of both electrode design and the waveform applied to the electrode (intensity, frequency). Therefore, tolerability should be evaluated for each dose.

4. Safety considerations of different tES techniques

4.1. Conventional (bipolar) and 4x1 montages

The modern development of tDCS (Nitsche & Paulus, 2000, 2001; Priori, 2003), and then related low-intensity tES techniques such as tACS (Antal et al., 2008), used an electrolyte (saline) saturated sponge “pocket” around a conductive rubber electrode, which was in turn connected by a lead to the stimulator (DaSilva et al., 2011). Conventionally, two electrodes were used, one cathode and one anode. Variations in this approach include changing sponge electrode size and shape (Nitsche et al., 2007). Approaches using more than two electrodes were considered but the size of electrodes limited their number and proximity on the scalp (Angius et al., 2018).

For a given current applied to an electrode, the current density increases proportionally with decreased electrode size, and for this reason, it was assumed that stimulation with small electrodes would not be tolerated. However, in 2008, this was overturned by delivering 2 mA tDCS with ~4 cm² electrodes, with the key design factor being the material and shape rather than the surface area of the electrode (Minhas et al., 2010). For example, the HD-tDCS[®] system uses specialized hydrogel. With smaller electrodes, it is possible to create montages with electrode arrays, including one electrode surrounded by a ring of electrodes of the opposite polarity (Laplacian montage as used in HD-tDCS[®] (Datta, Bansal, et al., 2009)) as all bipolar montages (Hannah et al., 2019; Rawji et al., 2018). HD-tDCS[®] is not less tolerated than conventional bipolar tDCS and high currents have also been tested for HD-tDCS[®] (Reckow et al., 2018), as well as various tES waveforms, such as tACS (Grover et al., 2022; Helfrich et al., 2014) or otDCS (Manojlović et al., 2025). Therapeutic neuromodulation trials with HD-tDCS[®] also followed (Caparelli-Daquer et al., 2012; Kuo et al., 2013).

Modeling software can be used to optimize the number of electrodes (multi-channel application), their size and placement, and the current per electrode (Dmochowski et al., 2011; Nishimoto et al., 2024; D.-W. Zhang et al., 2022) for both superficial and deep brain targets (Antonakakis et al., 2024; Huang & Parra, 2019). Some approaches like tTIS depend on the use of precisely placed smaller electrodes. Smaller electrodes also support the use of head-gear combining tES and EEG.

Conclusions and recommendations: The 4x1 montage (e.g., used for HD-tDCS[®]) has the same safety profile as conventional bipolar tES. The selection of sponge pad or gel-based electrodes depend on the trial hypothesis, brain targeting constraints, and practical factors

4.2. tACS

tACS continues to demonstrate a favorable safety profile when used within typical experimental and clinical parameters. As previously reported, sensations under the electrodes are generally less intense than during tDCS (Fertonani et al., 2015). This may be due to reduced electrochemical effects and the frequency-filtering properties of neuronal membranes (Deans et al., 2007). Phosphenes and cutaneous sensations are most pronounced at frequencies between 10 and 30 Hz, with a peak around 20 Hz, and tend to diminish at both lower and higher frequencies (Turi et al., 2014). Phosphenes are more prominent with frontal montages, while skin sensations increase with central montages. Both effects scale with intensity (Raco et al., 2014).

Since the last review, multiple studies have confirmed the absence of SAEs in both healthy and clinical populations across a wide range of standard tACS protocols (Evans et al., 2019; Indahlastari et al., 2018; Matsumoto & Ugawa, 2017). Structured assessments consistently report SEs such as transient sensations such as tingling, itching, phosphenes and only mild AEs (Grade 1), including mild headaches (Daughters et al., 2020; Kvašňák, 2019; Zeng et al., 2019). These effects are generally short-lived and often reported at comparable rates in sham conditions (Bland & Sale, 2019). Studies using intensities of up to 2 mA baseline to peak and durations of 20 to 40 minutes per session, administered across multiple days, have demonstrated consistent tolerability in both experimental and clinical settings, including in patients with depression (Alexander et al., 2019) and substance use disorders (Daughters et al., 2020).

Conclusion and recommendation: Current evidence shows that tACS is safe and well tolerated when applied within standard parameters. Across healthy and clinical populations, only mild AEs (Grade 1) and transient SE typically dependent on stimulation frequency and montage, have been reported, with

incidence rates often comparable to sham, and did not require medical care nor necessitate early termination.

4.3. Oscillatory tDCS

Oscillatory transcranial direct current stimulation (otDCS) is a form of tES that combines features of both tDCS and tACS. It involves the application of low-intensity sinusoidally modulated currents with a direct current offset. This means that the current oscillates at a specific frequency while for each electrode remaining entirely within either the positive or negative polarity range (i.e., either anodal or cathodal) and intensity within the standard range (i.e., between 1 and 2 mA). Given that otDCS incorporates elements of both tDCS and tACS, its safety profile may be expected to be similar to those of these established techniques. A recent study compared the subjective experience (tolerability) and SEs of tDCS (1.5 mA), tACS (0 ± 1 mA, i.e., 2 mA peak-to-peak), and otDCS (1.5 ± 0.5 mA, i.e., between 1 and 2 mA) in healthy young adults (Bjekić et al., 2024). The findings indicated that otDCS induced discomfort levels comparable to tDCS while producing similarly mild but somewhat less frequent AEs, including scalp itching (31.0% post-tDCS, 26.2% post-otDCS), tingling sensations (42.9% post-tDCS, 23.8% post-otDCS), and mild scalp irritation (28.6% post-tDCS, 16.7% post-otDCS). SEs typically associated with alternating currents, such as phosphenes, were reported by three participants during tACS and one during otDCS, while shaking of the visual field was reported during tACS only. Specific to otDCS, a negligible-to-mild burning sensation was reported by 14.3% of participants, while 19.1% experienced increased tiredness following stimulation. This sham controlled study delivered otDCS as well as tACS and tDCS via electrodes placed on the left parietal cortex (P3) and contralateral cheek while the frequency was in theta range (4–8Hz) for otDCS and tACS. The same profile of AEs was reported in other studies that applied theta-band otDCS (Vulić et al., 2021; Živanović et al., 2022), while there are no available reports on protocols in other frequency bands.

Conclusions and recommendations: Current evidence suggests that otDCS, like tDCS and tACS, is safe and associated with minimal AE (Grade 1) when applied within standard parameters. However, research on otDCS remains limited, and several factors—including electrode positioning, current intensity, and stimulation frequency—may influence its tolerability. Additionally, the long-term effects of repeated otDCS sessions, particularly in individuals with neurological conditions, remain unexplored.

4.4. tRNS

Transcranial random noise stimulation (Bikson et al., 2019) is mostly used with frequencies between 100–640Hz (Terney et al, 2007), has been recognized for its good safety profile, with AEs comparable to sham. tRNS includes symmetric biphasic waveforms (with zero DC) and asymmetric waveforms including monophasic or DC offset (Mondino et al., 2022; Murphy et al., 2020; Tokikuni et al., 2024).

Sheffield et al. (2022) analyzed AE data from 1,019 healthy adults who underwent 9–11 daily sessions of tRNS, tDCS, or tACS using small circular electrodes (3.14cm^2) centred on four different cortical target sites. Using Bayesian statistics, they found support for the null hypothesis, indicating that AEs were similar between active and sham tRNS. Additionally, blinding data revealed excellent blinding efficacy for tRNS. These findings align with previous studies using fewer sessions and larger sponge electrodes, which also reported no significant differences in AEs between tRNS and sham, as well as advantages such as higher cutaneous perception thresholds and lower AE reporting rates compared to tDCS (Ambrus et al., 2010). A notable finding is that AEs (Grade 1) varied by stimulation and collection site, suggesting the potential influence of training differences or population characteristics on reported AEs (Sheffield et al., 2022). However, no longer-term data are provided.

Large-scale studies on clinical populations remain limited, although the reported AEs (Grade 1) are similar to those ones reported in healthy adults. tRNS has been used in multiple studies on adults with tinnitus, with a recent review reporting only mild AEs (Alashram, 2024). However, AE variability across studies mirrors the SE observed by Sheffield et al. (2022), which may be attributed to different experimenters' expertise or types of population.

For individuals with brain damage, preliminary evidence suggests no reported AEs with tRNS. In a study investigating vision recovery in patients with cortical blindness due to V1 damage, the patients did not report any AEs (Herpich et al., 2019).

Most paediatric studies have focused on atypically developing children. A recent study examined 1,032 tES sessions in children and adolescents with neuropsychiatric and neurodevelopmental disorders (Battisti et al., 2025), confirming effective blinding, consistent with earlier paediatric research (Dakwar-Kawar et al., 2022, 2023; Looi et al., 2017; Splittgerber, Suwelack, et al., 2020). Although AEs were similar between active and sham tRNS, an overall higher AE (Grade 1) reporting rate for tRNS compared to tDCS (including both sham and active conditions) was noted. This discrepancy is unlikely to stem from tRNS, and is likely to be due to differences in participant populations or experimenter effects. In animal models, juvenile mice underwent the same protocol as children with atypical development (nine twice-weekly sessions of 0.75mA (peak-to-peak) over one month) (Looi et al., 2017), with no detectable macroscopic tissue damage (Sánchez-León et al., 2021).

Research on home-use tRNS remains scarce. The only known study compared 20min AI-driven personalised current intensity tRNS, 1.5 mA (peak-to-peak) tRNS, and sham tRNS in healthy adults at home. No AEs (Grade 1) differences between active tRNS and sham were found, and the participants tolerated the intervention well (Cohen Kadosh et al., In press).

Conclusion and recommendation:: In summary, the existing evidence supports the safety and tolerability of tRNS in the lab and at home. However, most studies have used relatively lower current intensities (0.03mA/cm² in children, and mostly <0.318mA/cm² in adults). It is recommended to carefully test higher intensities, because it remains an open question whether higher intensities would maintain similar AE rates and blinding efficacy.

4.5. Network-targeted tES

Interest has grown in tES to modulate large-scale brain networks typically using multi-channel¹ tES— i.e., simultaneous stimulation of functionally or structurally connected regions that exhibit correlated activity across time (Ruffini et al., 2018). These networks are typically identified through fMRI (task-based or resting-state BOLD) (Fox & Greicius, 2010), (s)EEG (Bartolomei et al., 2018; Centeno & Carmichael, 2014), magnetoencephalography (MEG) (Cho et al., 2024, p. 202), and/or diffusion-weighted MRI (Babaeeghazvini et al., 2021). Examples include canonical networks such as the default mode network, salience network, and dorsal attention network (Zhou et al., 2018). Alternatively, networks may be defined as sets of brain parcels, based on standardized parcellations, supporting cognitive or sensorimotor functions (Lawrence et al., 2021; Schaefer et al., 2018; Wang et al., 2021).

Many studies end up stimulating networks by default due to the spatial scale of the electric field generated by typical electrode montages. However, this section specifically addresses network stimulation studies that have generated empirical data by explicitly targeting networks defined through functional or structural imaging modalities (Table S1). It excludes stimulation protocols characterized by broad, non-specific cortical coverage (Splittgerber, Salvador, et al., 2020; Sprugnoli et al., 2019), as well as approaches primarily aimed at suppressing activity within single epileptogenic zones (Daoud et al., 2022; Kaye et al., 2021; Simula et al., 2024). Epileptogenic zones can be conceptualized as networks due to the pathological synchrony observed across different regions and characteristic seizure propagation patterns (Daoud et al., 2025), and current efforts are investigating the potential of stimulating epileptogenic networks using multichannel tDCS (Ruffini et al., 2018). However, clinical data regarding safety and efficacy are not yet available.

The studies with network-based targets (Abellaneda-Pérez et al., 2021; Adhia et al., 2023; Dagan et al., 2018; Ester-Nacke et al., 2024, 2025; Fischer et al., 2017; Goede et al., 2024; Mencarelli et al., 2020; Salehinejad et al., 2025; Smeele et al., 2023; Wei et al., 2024, 2024; Y. Zhou et al., 2022) share protocol characteristics with potential safety implications: they often use smaller electrodes (contact areas < 8 cm²); they employ intensities commonly exceeding 2 mA and going as high as 4 mA (defined as the sum of the currents delivered through the anodes); and they generate diffuse EF distributions often optimized using algorithmic approaches to achieve network level targeting (Ruffini et al., 2014, 2018). Still, no SAEs have been reported, and only common AEs (Grade 1) are reported (e.g., tingling, itching, transient redness under the electrodes, and mild headaches). Studies comparing network-targeted protocols with

¹ Multi-channel is a misnomer referring to the use of three or more channels.

conventional montages, including tDCS and tRNS, report no significant differences in AEs and SE (Fischer et al., 2017; Mencarelli et al., 2020). One under-examined aspect is state dependence: the idea that stimulation effects may vary depending on ongoing brain activity (H. Luo et al., 2025). While not anticipated to raise safety concerns, state dependence may affect response consistency, including of pathological networks (Daoud et al., 2025; Schaper et al., 2023).

Conclusions and Recommendations: Network-targeted tES demonstrates minimal AEs (Grade 1) within the conventional parameters including intensities under 2.0 mA per-electrode and electrode contact areas higher than 3.14 cm². Montage optimization algorithms are recommended to optimize the EF distribution, especially in complex networks. There is no evidence for new potential safety issues with network stimulation that necessitate special standards.

4.6. Transcranial temporal interference stimulation (tTIS)

Transcranial temporal interference stimulation (tTIS) is designed to target deeper brain structures in humans with good depth-focality trade-off (e.g., (Beanato et al., 2024; Hummel & Wessel, 2024; Kurtin et al., 2025; Vassiliadis et al., 2024; Violante et al., 2023; Wessel et al., 2023)), demonstrating a favorable safety profile when used within conventional parameters. Studies have consistently reported minimal AEs, while no SAEs have been documented.

Typically, stimulation parameters for tTIS include carrier frequencies ranging between 1,000–20,000 Hz, beating envelope frequencies between 5-130 Hz and currents usually up to approximately 4 mA peak to peak with session durations commonly around seconds to minutes. Most frequent AEs, expected from tES, were perceived sensations such as tingling, burning, itching ((Vassiliadis et al., 2024) for review (Demchenko et al., 2025)). The perception of stimulation-induced sensations has been shown to depend directly on stimulation intensity, becoming more noticeable as the current is approaching higher thresholds, e.g., around 2 mA (Vassiliadis et al. 2024). It has been demonstrated that the perceived sensations are comparable between the temporal interference condition and control conditions, including a high-frequency control (with no difference between carrier frequencies) and conventional sham (involving fade-in and fade-out stimulation) (Vassiliadis et al. 2024b). This renders tTIS as a method with excellent blinding opportunities well suited for double-blinded and placebo-controlled trials. A recent meta-analysis (Demchenko et al., 2025) suggests that perceived mild sensations like tingling, itching, though rather rare, might be more frequently reported in verum tTIS (11%) compared to control (5%), an important aspect that must be further explored. Rarely, subjects describe headache, sleepiness/drowsiness, nausea or pain. However, these AEs are comparably frequent during tTIS and control stimulation (Demchenko et al., 2025).

Studies that directly assessed the safety profile of tTIS, such as the detailed examination by Piao *et al.* (2022) and Wang et al. 2024, have reinforced its general tolerability and absence of significant AEs. Piao et al. (2022) and Wang et al. (2024) investigated 38 and 88 healthy subjects, respectively, monitoring neuropsychological, electrophysiological, and behavioral parameters, including serum NSE levels and EEG, and lent additional support for tTIS's favorable safety profile.

First applications in patient cohorts confirmed a favorable safety and AEs profile of tTIS (e.g., (Lamoš et al., 2025; Missey et al., 2025; Ploumitsakou et al., 2025; Vassiliadis et al., 2024; Yang et al., 2024)) .

However, the long-term safety profile and the effects of repeated or prolonged applications remain incompletely evaluated and have to be addressed in upcoming studies.

Conclusion and recommendation: tTIS using carrier frequencies of 1,000-20,000 Hz and currents ≤4 mA peak-to-peak (single studies up to 30mA) is currently regarded as safe for use in both basic neuroscience and early clinical-translational research, with only mild AEs reported (Grade 1). Initial clinical applications support this favorable safety profile. Notably, tTIS provides strong potential for effective participant blinding, a key advantage in experimental design. Continued, rigorous monitoring of AEs remains essential—particularly as stimulation protocols are refined and new ones developed, patient populations are included, and long-term safety is assessed and needs to be demonstrated. Overall, the safety profile of tTIS is comparable to that of other established NIBS techniques, such as tACS.

4.7. Transcutaneous spinal direct current stimulation (tsDCS)

During transcutaneous spinal DCS (tsDCS) (Cogiamanian et al., 2008), electrical current is delivered through an electrode positioned on the skin over the spinal cord with the return electrode placed over various regions according to different protocols (mainly the shoulder, the anterior aspect of the trunk, or along the spine). tsDCS appears to influence ascending and descending spinal pathways and to modify the excitability of various spinal reflexes in humans and animals (Priori et al., 2014). In general, anodal tsDCS tends to suppress conduction along spinal pathways and to facilitate reflexes, while cathodal tsDCS tends to enhance responses mediated by spinal ascending pathways and inhibit reflexes.

In several clinical trials including patients with neuropathic, musculoskeletal, or visceral pain the analgesic effect of tsDCS was proven (thoracic anode placement; 2,5 mA, 20 min, at least 5 days stimulation) (Guidetti et al., 2021; Hodaj et al., 2023). The mechanisms underlying the analgesic effects of tsDCS remain largely unknown. However, in healthy subjects, the technique likely modulates synaptic efficacy at the segmental level, influencing the local processing and/or transmission of nociceptive inputs in the dorsal horn (Lenoir et al., 2018). Interestingly, anodal tsDCS reduced reactive oxygen species (ROS) levels and increased antioxidant capacity markers such as glutathione (GSH) and total antioxidant capacity (TAC), suggesting improved mitochondrial efficiency in multiple sclerosis (MS) (Mrakic-Spota et al., 2025).

Clinical experience and the available reports suggest that tsDCS does not induce SAEs. Computational simulations support this insight (Guidetti et al., 2023), also in presence of metallic spinal implants (Kuck et al., 2019), as induced electric field values are reported to be over a thousand times lower than the safety thresholds for tissue injury (Bikson et al., 2009). While one study reported no blood biomarkers indicative of neuronal damage following stimulation (Cogiamanian et al., 2008), a preliminary account (H. Zhao et al., 2023) indicates that the most frequently AEs are mild sensations of burning, tingling, and itching below the stimulating electrodes. Skin redness may occur, however, this tends to be transient and self-resolving. Thus, tsDCS does not induce changes in bodily state, at least as measured by autonomic nervous system metrics.

Conclusions and recommendations: Carefully inspect the spine for vertebral malformations (e.g., spina bifida, myelomeningocele) as these can alter the electrical environment of the spinal cord, affecting current flow during tsDCS. Syringomyelia can also significantly alter the pattern and effectiveness of current flow during tsDCS due to the presence of a fluid-filled cavity in the spinal cord, which changes local conductivity and may shunt current away, therefore careful consideration of individual anatomy and possible adjustment of stimulation protocols are necessary in patients with spine abnormalities and syringomyelia. No safety data exist for pregnant women and for patients with implanted active devices in the torso (injection pumps, stimulators, cardiac pacemakers, etc). For these cases, no specific safety recommendation is made but study-specific risk analysis is warranted.

4.8. Optic nerve/retina stimulation

During repetitive transorbital alternating current stimulation (rtACS) a weak electrical current is delivered to the eye through a pair or multiple electrodes attached to the skin around the eye. Animal studies using crush and transection models of the optic nerve indicate that the electrical stimulation induces structural and functional neurorestoration (axonal regeneration, normalised visual evoked potentials), and has a neuroprotective effect (better survival of ganglion cells) (Miyake et al., 2007; Morimoto et al., 2005; Tagami et al., 2009; Yin et al., 2016). These processes are assumed to be mediated by the release of neurotrophic factors and increased chorioretinal blood flow (Fu et al., 2015).

In the previous version of these guidelines (Antal et al., 2017a, p. 201), we reported on the safety and tolerability outcomes from studies involving 760 patients with optic neuropathies, such as those following stroke or with post-chiasmatic lesions, who were treated in various clinical trials using this technology (Fedorov et al., 2011; Gall et al., 2013, 2010, 2016, 2011, 2015; Sabel et al., 2011; Schmidt et al., 2013). The most common AEs were mild skin sensations and irritation, headache, drowsiness, and sleep disturbances. No stimulation-related SAEs were reported.

Since 2017, the number of clinical trials using rtACS has been limited. In one study (Räty et al., 2021), 56 patients with occipital stroke were stimulated using 5-15 Hz rtACS, or with the combination of occipital tDCS and rtACS. No serious AEs occurred. The most common AEs were mild skin irritation under

stimulation electrodes during the treatment, tiredness, 'other' skin sensations (about 30-100% of the cases, depending on the experimental setup), mild headache, and phosphene-like visual phenomena (about 30%). A low number of patients (maximum 2) reported metallic taste, myokymia, dizziness, sleeping difficulties (only in the sham group), and lack of concentration (only in the sham group). No difference in the frequency of any of the reported AEs, nor in their composite number per subject was detected between the different modalities.

A recent review of 10 RCTs and 15 observational studies, including transcorneal electrical stimulation, transpalpebral electrical stimulation, transdermal electrical stimulation, and rtACS, reported no SAEs (J. Liu et al., 2021). Minor complications included foreign body sensation, dry eye, transient superficial keratitis, cutaneous sensation at electrode sites, and mild headache in sporadic cases.

An interventional, randomized study on 51 patients using transcorneal electrical stimulation reported mild AEs, including predominantly dry eye symptoms, but also a few cases of ocular discomfort, ocular pain, transient visual disturbance, increased tear production, and itching (Stett et al., 2023).

Two studies using rTACS to target phosphene induction in 15 (Sabel et al., 2021) and 61 (Hunold et al., 2025) healthy participants, respectively, reported that the stimulation was well tolerated and no AEs occurred.

An alternative terminology for transorbital stimulation is retinofugal alternating current stimulation (rACS) targeting α -oscillations in the visual cortex via periorbital electrodes (Haberbosch et al., 2019). In this study, multichannel stimulation was applied at 10 Hz, with an amplitude of 120% phosphene threshold (resulting in 351.69 μ A peak-to-peak). Topographical modeling revealed the highest current densities in the anterior visual pathway, the retina, and the optic nerve. No serious AEs occurred in 20 healthy subjects, and the stimulation was well tolerated.

An ongoing multicenter clinical study in Germany is investigating the efficacy of the rtACS in open-angle glaucoma (Schittkowski et al., 2025). As of the publication date of this paper, no safety-related concerns have been reported.

Another stimulation form, using a rectangular waveform, is also applied to treat glaucoma. This type of stimulation is described as optic nerve stimulation (ONS) (Erb et al., 2022). In a recent study, seventy glaucoma patients with progressive vision loss underwent electrical ONS (5-35 Hz), with stimulus intensities up to 1.2 mA, for 10 days, about 80 minutes of stimulation/day. In this paper, no AEs or SAEs were reported.

Conclusions and recommendations: Based on the published data, the likelihood of detrimental effects using rtACS is extremely low and not different from other protocols using tES. It is recommended that personalised protocols (e.g. slightly below phosphene threshold intensities) are used at least at the beginning of the treatments. Furthermore, RCTs are needed to establish the optimal protocols for the application to different kinds of visual disorders.

4.9. Cerebellar stimulation

Cerebellar tES, including tDCS, tACS and tRNS, has emerged as a non-invasive technique targeting cerebellar networks implicated in motor control, cognition, and affective regulation. While its therapeutic and experimental applications are expanding, the safety profile of cerebellar tES remains an important topic for clinical and research deployment.

Systematic reviews and individual randomized controlled trials indicate that cerebellar tES administered within established current intensity ranges from 1 to 2 mA and ≤ 30 minutes per session is safe and well tolerated in healthy adults and patient populations (Manto et al., 2022; Warthen et al., 2024).

In a recent meta-analysis of 14 studies involving cerebellar tDCS in patients with degenerative ataxia (N = 406), no serious AEs were reported; only mild, transient SEs occurred in two studies (Gong et al., 2023).

Commonly observed AEs, as in cortical tDCS, include scalp tingling, itching, mild headache, skin redness, fatigue, and dizziness, these symptoms typically resolve shortly after stimulation and rarely necessitate treatment discontinuation (Antal et al., 2017a; Herzog et al., 2022).

Several trials combining cerebellar tES with motor rehabilitation in stroke survivors or individuals with balance disorders have similarly reported no serious complications. For example, in a controlled study applying cerebellar tDCS during virtual balance training in stroke patients, mild headache was the most

frequently noted symptom (Qurat-UI-Ain et al., 2023). Studies employing cerebellar tACS or tRNS also demonstrate good tolerability, with minor cutaneous or vestibular sensations but no severe neurological or systemic effects (Tavakoli & Yun, 2017).

Although, data remain limited; preliminary trials indicate that cerebellar tES is generally well tolerated in adolescents with neurodevelopmental disorders (D’Urso et al., 2021): the anatomical proximity of the cerebellum to the brainstem warrants conservative dosing and individualized current modeling to avoid off-target stimulation. Ethical aspects and regulatory oversight are essential when applying tES in pediatric populations (Salehinejad et al., 2022).

There is no single standard for cerebellar stimulation electrode placement, which is usually guided by previous research (Ferrucci et al., 2015). Stimulation sites vary by function, for example in stroke rehabilitation: superior-lateral cerebellum for motor tasks, pharyngeal area for dysphagia, and lobule VII for aphasia, contralesional stimulation is often more effective due to crossed cerebro-cerebellar pathways, and bilateral stimulation has shown greater enhancement of swallowing function compared to unilateral, likely due to increased input to the cerebral swallowing cortex (Liu et al., 2024).

Conclusion and recommendation: cerebellar tES—when delivered within conventional parameters—is a safe and well-tolerated neuromodulatory intervention in adult populations. No serious AEs have been documented to date. Mild, transient SEs are common and manageable. However, further studies are required to assess the long-term safety of repeated or chronic cerebellar stimulation, particularly in vulnerable populations such as children or individuals with neurological comorbidities. From a procedural perspective, it is recommended to use montages that place the active electrode over the cerebellar hemisphere (whole or lateral) — typically located 1 cm below and 2 cm lateral to the inion— and the reference electrode at an extracephalic site, such as the ipsilateral shoulder. This configuration is proposed to reduce current spread to brainstem structures (Parazzini et al., 2013).

5. Safety considerations of repeated tES application

5.1. Repeated /multiple sessions across days

The rationale for delivering tDCS across multiple days is to enhance its efficacy and promote longer-lasting neuroplastic after-effects. In line with this objective, numerous studies over the past two decades have investigated the efficacy and safety of multi-session tDCS protocols.

A key meta-analysis conducted by Bikson et al. (2016) assessed the safety of repeated tDCS interventions, defined as more than four sessions per week, drawing on data from over 1,000 participants. The analysis confirmed the safety and tolerability of repeated tDCS, reporting no SAEs. Subsequent studies applying up to 10 tDCS sessions per subject in controlled clinical or research settings, and administered by trained personnel, have consistently replicated this safety profile (Antonenko et al., 2022, 2024; Choy et al., 2023; Juras et al., 2025; Ke et al., 2023; Talsma et al., 2017; Teixeira-Santos et al., 2022). A comprehensive meta-analysis of 158 studies ($n = 4,130$) further confirmed that AE rates did not increase with cumulative tDCS exposure—defined as two or more sessions spaced no more than a day apart—nor did they differ across diagnostic groups, reinforcing the safety of repeated tDCS protocols (Nikolin et al., 2018).

The use of home-based tDCS has expanded the feasibility of long-term interventions, enabling daily stimulation protocols extending over several weeks or months (Grønli et al., 2022; Im et al., 2019; Madhavan et al., 2025a; Martens et al., 2018). For instance, Martens et al. (2018) administered a 4-week daily tDCS intervention (2 mA, 20 minutes/session, 5 sessions/week; 20 sessions total; ~400 minutes per subject) targeting the left DLPFC in 27 patients with chronic minimally conscious state. No SAEs were observed in the active tDCS group. One SAE (epileptic seizure) occurred in the sham group on day 4, though this event was deemed unrelated to stimulation, as the sham protocol involved only 5 seconds of active stimulation (5 s ramp-up, 5 s stimulation, 5 s ramp-down).

In another study, Im et al. (2019) evaluated the efficacy of a 6-month home-based tDCS protocol in 20 patients with AD, with 12 receiving active and 8 receiving sham stimulation (2 mA, 30 minutes/session; ~182 sessions; ~5,460 minutes total per subject; bilateral DLPFC montage: anode over F3, cathode over F4). No information on AEs or SEs was reported. Nonetheless, 18 of the 20 participants completed the study; the two drop-outs were attributed to refusal or caregiver-related issues rather than stimulation-related AEs.

Further home-based studies have supported the safety and tolerability of long-term tDCS. In amyotrophic lateral sclerosis (ALS) patients, Madhavan et al. (2025) administered 72 sessions over 24 weeks (2 mA, 20 minutes/session, 3 sessions/week; 1,440 minutes total per subject) without SAEs. Similarly, Grønli et al. (2022) applied daily tDCS for 18 weeks in AD patients (2 mA, 30 minutes/session, 7 sessions/week; ~122 sessions; ~3,660 minutes per subject), with no SAEs reported. Ghazi-Noori et al. (2024) conducted a 6-week study in patients with bipolar disorder (2 mA, 30 minutes/session; 21 sessions; 630 minutes total per subject), reporting that 90.6% of AEs were mild, 9% moderate, and only 0.4% severe. Mild AEs included isolated reports of tingling, burning sensation, itching, and skin redness.

Conclusions and recommendations: Multi-session tDCS delivered at conventional intensities (≤ 4 mA) by trained professionals in clinical or research settings remains well-tolerated, with no SAEs related to tDCS reported. Emerging data from home-based protocols, extending up to 5,000 minutes of total stimulation time, suggest initial safety under real-world conditions. However, to substantiate these findings, rigorously controlled trials with larger sample sizes and systematic AE monitoring are essential.

5.2. Safety considerations of repeated /multiple-sessions per day

Applying multiple tES sessions per day (also often referred to as an “accelerated protocol”, “intensive application” or “spaced tES” in the literature) builds on conventional protocols, which typically deliver stimulation once per day. Inspired by findings from accelerated repetitive transcranial magnetic stimulation (rTMS) studies, where multiple daily sessions have been shown to augment treatment effects, these multi-session-per-day tES protocols aim to enhance efficacy by increasing the frequency of sessions within a single day.

A potential concern with this approach is the increased risk of AEs due to the cumulative effects of stimulation. However, there is little evidence to suggest that intensifying the application schedule (to 2-5 sessions per day) and reducing the inter-session intervals (for several hours to 10-20 minutes) elevates the risk of serious AE. While participants receiving active tES appear to have a higher frequency of mild AEs associated with tES (such as burning sensations or itching) compared to sham, similar effects have been observed in conventional once daily protocols (Nikolin et al., 2018).

The literature search identified 70 studies ranging from case reports to randomized controlled trials, covering both healthy and pathological conditions. In total, these studies involved over 1,900 individuals and more than 14,000 active sessions.

Although few studies have directly compared the safety of once- versus multiple-daily tES protocols, available evidence from neurophysiological studies suggests that multi-session protocols do not substantially elevate the risk of serious AEs. These include consecutive tDCS sessions over the motor cortex spaced by short (3-20 mins) or long intervals (3-24 hours) compared to a single session (Monte-Silva et al., 2013), thrice-daily 20 min tRNS sessions spaced 30 mins apart (Brevet-Aeby et al., 2019), and twice-daily vs once-daily tDCS (20 min, 5 h apart) in patients with vascular depression (Zanardi et al., 2020).

The majority of studies retrieved in the literature search involve patients with neuropsychiatric conditions and compare multiple-daily tES protocols to sham. One of the earliest applications of a multi-sessions tES protocol was in patients with schizophrenia (Brunelin et al., 2012). These received twice-daily tDCS sessions, spaced 2 to 3 hours apart, with the anode placed over the left prefrontal cortex and the cathode over the left temporoparietal junction (ten 20-min sessions, 2 mA). While this study primarily investigated therapeutic outcomes, it also reported no significant AEs and preserved participant blinding. Subsequently, a meta-analysis of eight studies (329 participants) with schizophrenia showed no difference in all-cause discontinuation between twice-daily tDCS and sham groups (W.-L. Jiang et al., 2022). Safe use of twice-daily protocols has also been observed in numerous randomized sham-controlled tDCS trials across several other clinical populations using twice-daily protocols, including subacute stroke (Hsu et al., 2023), stroke (E. F. Pinto et al., 2021) Parkinson disease (Aksu et al., 2022; Dashtelei et al., 2024), tobacco use disorder (Mondino et al., 2022), obsessive compulsive disorder (Bation et al., 2019), major depression (Moirand et al., 2022), bipolar depression with suicidal ideation (J. Wang et al., 2024), social anxiety disorder (Jafari et al., 2021), epilepsy (Kaufmann et al., 2021), and acute respiratory distress syndrome (Andrade et al., 2022). These twice-daily session studies employed

varying electrode montages, session durations, and stimulation intensities (ranging from 9 to 30 minutes at 1–3 mA), as well as differing inter-session intervals (from 10 minutes to 6 hours).

Some recent studies have also explored delivering more than two tES sessions per day in clinical populations, with some protocols including up to five daily sessions. This intensified approach has been applied in patients with major depression (Couture et al., 2025), schizophrenia (Mondino et al., 2021), and catatonia (Bouaziz et al., 2023). Importantly, while most studies report only mild, transient effects (e.g., tingling, itching, redness), comparable to those observed with once-daily protocols, a trial of 29 patients with depression receiving 50 tDCS sessions (five per day, 20 min duration at 2 mA, 20 min inter session interval with left anodal/right cathodal DLPFC stimulation) found that 18 (62%) developed mild, persistent erythematous-squamous plaques under the anode, consistent with irritative contact dermatitis (Miron et al., 2023). Additionally, they reported high rates of redness at electrodes sites (100%), headaches (67.9%) and fatigue (57.1%). Notably, the authors reported that tDCS parameters, including current intensity and density, were within established safety guidelines, used saline pre-saturated electrode sponges ('SNAPPads'), and maintained impedance levels below 30 k Ω . These details suggest that poor technique or non-compliance with safety recommendations are unlikely to explain the observed AEs.

Conclusions and recommendations: Direct comparisons between multiple and once daily tES protocols regarding safety remain limited. Delivering up to five 20-min sessions per day (at 2 mA, separated by 20 min) is tolerable, with a safety profile comparable to once-daily tES protocols. Particular attention should be paid to potential skin reactions, and special care, including the use of optimized equipment, should be taken to minimize these effects. Given their safety profile, multi-sessions-per-day protocols may be particularly suitable for users who are unable or unwilling to attend multiple visits, as well as for those with severe cognitive or clinical symptoms who may benefit from more intensive treatment.

6. Summary of Side effects and Adverse events associated with low intensity tES in human studies

6.1. Perceptual Side Effects

At the perceptual level, commonly reported SEs remain scalp discomfort due to cutaneous sensations (i.e., somatosensory perceptions), such as tingling, itching, and burning. Recent evidence from a large body of tES literature, including studies using tDCS, tACS, tRNS, and HD-tDCS, supports that perceptual SEs are generally mild, transient, and well tolerated in both healthy individuals and clinical populations for intensities up to 2 mA. Some HD-tDCS studies have explored intensities up to 4 mA, where effects remain tolerable but perceptual sensations tend to be more pronounced. However, it should be noted that a considerable proportion of people receiving sham stimulation report similar perceptions too, warranting caution in attributing every occurrence to a tES effect.

Tingling is one of the most commonly reported sensations during tES and the sensation is typically localized at the site of stimulation (Bjekić et al., 2024; Chang et al., 2024; Fertonani et al., 2015). This sensation is generally mild and short-lived (Gairola et al., 2024; Hawas et al., 2025; Latrèche et al., 2024; Ruffini et al., 2024; Upadhyay et al., 2025; Wang et al., 2024). Numerous studies have reported tingling sensations in both active and sham conditions, with some studies noting a higher incidence in sham groups. However, the underlying reasons for this observation remain unclear (UI-Ain et al., 2024). Delicado-Miralles et al. (2024) also showed that tingling sensations were most prominent during the initial sessions and declined in frequency and intensity over time, highlighting habituation across repeated exposures. A large-scale analysis of 6,779 sessions of remotely supervised at-home tDCS (RS-tDCS) in clinical trial contexts reported no serious SEs and a very low session abort rate (0.04%), with the most common SE being mild tingling, itching, and warmth, equally distributed across active and sham conditions. Notably, no participants discontinued due to tolerability concerns (Pilloni et al., 2022). The prevalence of tingling in pediatric populations was also shown by Buchanan et al. (Buchanan et al., 2021), noting it was typically mild and not associated with dropouts.

Thus, **mild local pain** or **discomfort** at the stimulation site is also among the reported SE associated with tES, particularly during tDCS sessions (Bjekić et al., 2024; Pérez-Borrego et al., 2024). This discomfort is typically characterized by sensations such as burning, itching, or pressure beneath the electrodes and is

usually transient, subsiding shortly after the end of the stimulation. Several studies report that these sensations are more prevalent at the beginning of stimulation sessions and tend to decrease with repeated exposure (Bjekić et al., 2024; Delicado-Miralles et al., 2024). The intensity and frequency of local pain and discomfort are influenced by stimulation parameters, electrode type, and individual sensitivity (Bjekić et al., 2024). All these aspects can be addressed through strategies such as the use of ramp-up and -down protocols avoiding abrupt current onset, adequate electrode preparation, consistent saline/gel application (Fertonani et al., 2015).

Phosphene and “vibration” perceptions are mainly induced during tACS, particularly at frequencies in the alpha and beta range and current intensities ≥ 1 mA, remains an expected SE as consequence of visual (Schwiedrzik, 2009) or tactile systems stimulation (Zeng et al., 2019), and is not considered harmful, despite its impact on perception. Several studies have confirmed that phosphenes, while occasionally interfering with tasks, are non-distressing and mitigated through protocol adjustments (e.g., montage design).

These results are consistent with earlier findings (Antal et al., 2017a) and may vary with electrode positioning and whether current ramping is applied for tDCS. While in general, effects like phosphenes or tingling may impact task performance or engagement temporarily, they are not sufficient grounds to halt or contraindicate stimulation protocols, unless requested by the participant.

6.2. Adverse Events

Redness of the skin at the electrode site is an anticipated, though relatively infrequent non-serious event. This erythema is typically mild and often resolves within hours. Woodham et al. (2024) reported that 63.5% of participants in the active tDCS group experienced skin redness, compared to 18.5% in the sham group. Zhou et al. (2024) and Park et al. (2024) also found skin redness among the most frequent mild AEs, with no long-term consequences.

In home-based multichannel tDCS, similar effects such as scalp burning and skin irritation have been noted (e.g., Park et al., 2024), although they are infrequent and typically resolve spontaneously (Ruffini et al., 2024). Importantly, these effects rarely result in dropout, and adherence remains high across clinical and home-based trials when appropriate safety measures are implemented (Pérez-Borrego et al., 2024). In pediatric and adolescent populations, Ciechanski and Kirton (2017) and Buchanan et al. (2021) emphasized that such sensations were generally well tolerated and did not lead to increased dropout, supporting the safety of tES across age groups. These incidents have been associated with non-conventional protocols/equipment, reinforcing the importance of adequate device design and user training (for details see Section 10). Provided appropriate protocols, equipment, electrodes and skin preparation are used, skin injury is not an expected AE of low-intensity tES (Pilloni et al., 2021; Woods et al., 2016). Monitoring for skin integrity can help minimize local irritation and enhance tolerability (Ruffini et al., 2024; Woodham et al., 2024).

Fatigue is a less consistently reported AE of tES. It has been described in some studies, though often without a clear association with active stimulation. Sleepiness and general tiredness have been reported in both active and sham conditions, suggesting non-specific origins potentially related to session timing, individual baseline state, or expectations (Latrèche et al., 2024; Woodham et al., 2024). In fibromyalgia and schizophrenia studies, fatigue was sometimes reported but did not significantly differ between active and sham conditions (Lyu et al., 2024; Yang et al., 2024).

In one experiment, intended alterations, including **dizziness**, motion perception shifts, and spatial disorientation, have been reported with tACS at low frequencies (1–2 Hz, 2.5 mA) in healthy individuals. These effects appear to be frequency-dependent and due to the modulation of the vestibular system function (S. Rossi et al., 2023).

Headaches are another reported AE across both tDCS and tACS protocols. These are generally mild, often occur during or shortly after stimulation, and tend to be self-limiting (Y. Chen et al., 2024). Studies such as those of Woodham et al. (2024), Wang et al. (2024), and Zhou et al. (2024) observed similar rates of headaches in both active and sham groups, suggesting that while common, headaches may not be directly induced by stimulation. Similarly, in a double-blind pilot trial of at-home remotely supervised tDCS (RS-tDCS) for veterans with persistent post-traumatic headache, no AEs were reported, and the

intervention resulted in significant reductions in headache days and severity, further supporting the safety and potential of RS-tDCS in populations with high symptom burden (L. Charvet, Harrison, et al., 2023). Similarly, Park et al. (2024) found that headaches were reported by 40.9% of participants in the active group and 19.0% in the sham group, with no statistical significance, reinforcing the notion that these effects are often nonspecific and mild.

Regarding **cognitive AEs**, there is no clear evidence that tES causes long-term or significant cognitive impairments. However, a few studies have reported short-lived mild AEs, affecting non-targeted functions, such as reduced attention, impaired concentration, and increased mental fatigue (e.g., (Yuan et al., 2022)). These effects were primarily self-reported and listed in specific populations, such as older adults and individuals with medical conditions undergoing prolonged or repeated stimulation protocols. On the other hand, when tES is applied to modulate cognition by down- or up-regulating cortical states, the intended effects arise from the modulation of cortical excitability, which can interfere with non-targeted functions, such as practice effects or learning. This suggests that tES may, in some cases, influence cognitive engagement indirectly rather than directly impairing it (e.g., (Leaver, 2025)). Reports of cognitive AEs remain rare, typically self-reported and not performance-limiting.

However, while most cognitive outcomes in studies are still tied to the primary stimulation target and interpreted as functional neuromodulation rather than AEs, the challenge of capturing off-target or secondary cognitive effects remains.

Conclusion and recommendations: tES is generally safe and well tolerated, with no evidence of serious or persistent SEs or AEs in healthy or sensitive populations when standard safety protocols are followed. The most common events are typically mild, short-lived, and manageable (AEs grade 1). Their occurrence can be reduced through technical adjustments, user education, and proper electrode application. Routine monitoring and reporting of these effects are recommended to refine individual tolerability profiles and assess any potential trade-offs in cognitive function. These effects do not pose a barrier to experimental, clinical or home-based use of tES. The summary of SE/AE is presented in Table 1

<<Table 1 about here>>

6.3. The association between ANS and tES

The autonomic nervous system (ANS) regulates involuntary functions such as heart rate, blood pressure, and respiration. It is closely connected to the brain via structures like the nucleus of the solitary tract, which integrates afferent signals — many of which travel through the vagus nerve—and coordinates responses through cortical and subcortical circuits. Given this brain–ANS–vagus integration, it is essential to consider how tES may modulate autonomic function (Makovac et al., 2017) and whether this may result in potential AEs. Based on the reports, tES (tACS, tDCS, tRNS) is safe for ANS function, with no reported AEs or impairments in cardiovascular or other ANS parameters. For example, tACS did not modulate pain-related autonomic responses, which was confirmed by Bayesian statistics (May et al., 2021; Prim et al., 2019). Also an extracephalic (arm/shoulder) electrode positioning in tDCS, one targeting M1 (Santarnecci et al., 2014) and the other one targeting the frontal midline (Vandermeeren et al., 2010) suggest null or mild effects on autonomic functions. Li et al. reported a transient increase in automatic arousal at the end of the tDCS session, an effect that disappeared afterwards (Z. Li et al., 2024). These results highlight that stimulating the brain through tES has no AEs at the level of ANS functioning.

In fact, only after applying tDCS, several studies suggest potential benefits on ANS functioning, such as transient improvements in heart rate variability (HRV), which reflects better autonomic regulation (Ko et al., 2024). Razza et al. (2024; (Razza et al., 2024)) recently showed a dose-dependent effect of tDCS for HRV, with stronger effects on HRV increases after 3 mA as compared to 1.5 mA. This ANS functioning has increasingly been employed as a supportive physiological marker in tES research, complementing behavioral and cognitive outcomes. For example, the stimulation of the DLPFC with tDCS has been shown to modulate ANS processing without reliably altering self-reported mood (Mondino et al., 2015), suggesting subtle, yet meaningful physiological shifts. Similarly, Schroeder et al. (2015; (Schroeder et al., 2015)) reported reduced autonomic arousal during emotional tasks following anodal tDCS over the left

prefrontal cortex, reductions linked to distraction and mild behavioral improvements. Recently, Allaert et al. (2022;(Allaert et al., 2022)) also demonstrated that active (vs. sham) tDCS over the left DLPFC was associated with decreased skin conductance responses, indicative of lower emotional arousal during emotion regulation. These findings suggest that HRV and other ANS indices may not only reflect the physiological effects of tES but also serve as potential biomarkers of treatment response or even therapeutic targets, particularly in conditions marked by dysregulated autonomic function.

Conclusion: The tES induced effects on ANS appear to be reversible, within normal physiological bounds, and in line with expected neuropsychophysiological patterns—raising no safety concerns. Long term SEs have not been reported. However, research on the autonomic effects of other NIBS modalities, such as tACS and tRNS, remains limited and warrants further investigation.

7. Safety considerations in neurotypical adults and special populations

7.1. Absolute and relative exclusion criteria for tES in non-clinical settings

In research involving healthy participants, particularly in basic and translational neuroscience research, it is essential to adhere to clearly defined inclusion and exclusion criteria in order to on one hand minimize potential risks and ensure participant safety and, on the other, ensure methodological rigor and exclude potential confounds.

By definition, the **inclusion criteria** for studies in healthy adults are the absence of neurological, psychiatric, or neurodevelopmental conditions and legal adulthood status (age of majority is ≥ 18 years in most countries, for detailed consideration of tES application in children and older adults see Section 7.3. and 7.4.), as well as no implanted electronic or metallic devices (e.g. deep brain stimulators, cochlear implants, pacemakers or metal plates in the head) and no uncontrolled seizures and/or seizure activity in the past year.

Exclusion criteria are typically categorized as absolute or relative, depending on the nature and severity of the associated risks. **Absolute exclusion criteria** refer to conditions that categorically disqualify a participant from taking part in a study due to the known potential for harm or significantly increased risk. The absolute exclusion criteria (i.e. contraindication) for tES application are open wounds, preexisting skin abnormalities (e.g. nevi, angiomas or previous burns/scars, neurodermitis, etc.), or active infection at the stimulation site, which could be conducive to or lead to increased risk of skin irritation, damage, or secondary infection associated with tES and/or the use of conductive gel/paste/solution.

Other exclusion criteria may apply depending on the study aims, available resources and overall cost-benefit analysis. These are **relative exclusion criteria** that do not have documented safety risks but are applied based on the principal investigator's decision either for precautionary or methodological reasons. For a conservative approach the following relative exclusion criteria can be applied: self-reported history of epilepsy or seizures, given the theoretical risk that modulation of cortical excitability may lower the seizure threshold - nevertheless, based on the available evidence, seizures have not been reported as an AE associated with tES; self-reported history of head or spine injury and/or surgery, which may alter brain structure or excitability, thereby increasing unpredictability of response to tES; current use of medications or drugs such as antidepressants, antipsychotics, or stimulants; self-reported history of persistent SE/AE that could be associated with tES, e.g. frequent headaches and migraines; tattoo at the stimulation site, as it would require consideration of the ink used (Maas et al., 2021); excessive scalp sensitivity and discomfort during electrode placement; possible pregnancy (for detailed consideration see Section 7.2.); low tolerability of previous NIBS applications, etc. Further common relative exclusion criteria in studies that aim to explore basic neuromodulatory mechanisms and effects of tES in neurotypical adults include factors that may act as confounds and add to the variability of outcomes, such as: excessive caffeine intake; smoking; alcohol, or recreational drug use; sleep deprivation before or severe fatigue on the day of the session; high scores on screening questionnaires for anxiety, depression, or distress, which may influence placebo/nocebo responses or AE reporting. Other relative exclusion criteria may be introduced depending on the specific study methods, aims and objectives.

7.2. tES in pregnant and breastfeeding or not-breastfeeding postpartum women

So far, nine studies have been published about tES during pregnancy, including tDCS (Kurzeck et al., 2021; Laurin et al., 2022; Shenoy et al., 2015; Sreeraj et al., 2016; Strube et al., 2016; Vigod et al., 2019; Q. Zhao et al., 2022), TNS (Trevizol et al., 2015), and tACS (Wilkening et al., 2019). Among these, only two RCTs were published: Vigod et al. (2019) observed the effect of 10 tDCS sessions delivered between 14-32 weeks of gestation and Zhao et al. (2022) observed the effect of one tDCS session pre-c-section. The remaining evidence comes from case studies encompassing 85 women receiving active stimulation, 83 of whom underwent tDCS.

Based on the current evidence, tES - particularly tDCS - appears to be well-tolerated during pregnancy, with minimal AEs reported. tDCS was used as an add-on treatment to loperidone (12-mg/day; Shenoy et al., 2015), to lamotrigine (100-mg/day; case report 1 from Laurin et al. 2022) and to Venlafaxine (75-mg/day, case report 2 from Laurin et al. 2022). Zhao et al. (2022) also reported tDCS concomitant with lumbar anesthesia (Bupivacaine only [n = 52] or Bupivacaine with Lidocaine [n = 10]) with no AEs due to the combination between tES and medication being reported.

As in the general population, studies present only transient mild AEs (tingling, itching and mild burning sensations at the application site, transitory experience of phosphenes, mild headache during and right after stimulation, dizziness and insomnia [probably unrelated to tDCS], difficulty in concentrating (Kurzeck et al., 2021; Laurin et al., 2022; Shenoy et al., 2015; Sreeraj et al., 2016; Wilkening et al., 2019; Q. Zhao et al., 2022)). One preterm birth was reported (Vigod et al., 2019), but no direct association with tDCS was established. No other neonatal complications were noted.

These findings suggest that tES has a benign safety profile during pregnancy and that the risk of fetal exposure to electric current is negligible. In a comparative perspective, modeling studies in ECT, which produces electric field densities approximately 100 times higher than tES, suggest that fetal exposure remains well within the safety limits set by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) (Bikson et al., 2023; Kibret et al., 2018). Consequently, it is reasonable to infer that tES, with its significantly lower electric field intensity, poses no additional fetal safety concerns. Furthermore, no major safety concerns for maternal health, fetal exposure, or newborn development have been reported at follow-up (between 24h after the intervention and up to 3 years after intervention), even when tES was used as an add-on treatment to medication (see Table S2).

In the postpartum period, evidence is limited. There is one case report of a depressed breastfeeding woman (Laurin et al., 2022) and an open-arm study (Griffiths et al., 2025) with 20 postpartum depressed women. In both studies tDCS was used as an adjunct treatment to antidepressants and the F3-anode, F4-cathode montage at 2 mA intensity was used. In both studies the acute treatment included 15 daily sessions across 4 weeks, followed by a maintenance treatment of three to four sessions a week for three to four weeks. Side and AEs reported were minor and transient, like those expected in the general population (mild fatigue, paresthesia of the scalp, mild headache). Hence, as tES does not enter systemic circulation, no risk of transmission through breast milk could be thought of. However, fatigue after tDCS sessions (an uncommon AEs) should be monitored in the postpartum, given that it could *in extremis* indirectly affect newborn care routines.

Overall, critical knowledge gaps persist on the reciprocal interactions between tES and reproductive/polypeptide hormones. Hormones such as progesterone, estrogen, luteinizing hormone, and follicle-stimulating hormone undergo significant fluctuations during pregnancy and the postpartum period, influencing cortical excitability and potentially modulating the physiological effects of tES. These hormonal shifts may hypothetically increase the vulnerability of women to seizures (Finocchi & Ferrari, 2011). Conversely, like rTMS, tES may also influence hormonal regulation, impacting neuroendocrine functions (e.g., (Aftanas et al., 2022)). Although fluctuating sex hormones during pregnancy or across the menstrual cycle may affect cortical excitability warrants further investigation, so far there has been no evidence that women are at increased risk when using tES in comparison to men.

Recommendations: tES, particularly tDCS may be considered a non-pharmacological treatment during pregnancy and postpartum, particularly for women who prefer to avoid, cannot use, or do not respond to medication, with informed consent addressing limited evidence. In both clinical and research contexts, pregnant and postpartum women, including those breastfeeding, should not be excluded by default if the benefit–risk balance is favorable. Protocols should monitor maternal health, fetal signals,

and infant outcomes, if possible. Future studies should collect reproductive, hormonal, and developmental data to better understand sex-specific effects of tES.

Precautions that should be considered with pregnant women: Avoid stimulation with an extracephalic electrode as there is no evidence in the literature about its effects. Do not stimulate directly over the abdominal/lumbar area (not part of standard tES protocols). After the 24th week of gestation, avoid stimulating in the supine position for theoretical concerns about dizziness and blood pressure drops due to compressing major blood vessels. For pregnant women either in clinical or research contexts, implement monitoring protocols that include frequent supervision by a specialized maternal health care team (especially when using home-based devices). Avoid stimulation when holding a baby/infant.

7.3. tES in pediatric populations

Since 2017, the number of tES studies in pediatric populations has significantly increased. In 2020, Zewdie et al. reported on a large-scale non-invasive brain stimulation study involving 384 participants who underwent at least one stimulation procedure. In total, 612 tDCS sessions were administered, including sessions with 92 children (12.9 ± 3.4 yrs). The intervention was well tolerated, with mild itching or tingling reported in 37% of participants. Other observed AEs included headache, neck pain, presyncope, tingling, combined itching and burning sensations, and nausea. Major reported AEs and the corresponding stimulation protocols in pediatric populations since Antal et al. (2017) are summarized in Table S3.

Recent reviews have demonstrated that tES is generally safe, with no AEs reported when established protocols are properly followed (Buchanan et al., 2021; Salehinejad et al., 2020, 2022). A more recent review by Salehinejad and Siniatchkin (2024) provides a comprehensive overview of the latest evidence on NIBS in pediatric populations. Consistent with findings from the past decade, data from the last two years (2022–2023) further confirm the safety of NIBS in children and adolescents when established protocols are strictly followed. Both tES and TMS are generally well tolerated, provided that safety guidelines, including exclusion criteria, are followed.

Computational models have indicated that the smaller cranial anatomy in pediatric populations will result in a higher brain electric field per applied current intensity (mA) (Kessler et al., 2013; Minhas et al., 2012). Predicted current densities were not higher at the skin, consistent with comparable tolerability. Differences in brain electric fields will depend on the montage and specific subject anatomy (eg. a minor with a relatively large head may be less sensitive than an adult with a relatively small head). Differences in electric field sensitivity are consistent with differences in dose response measured by changes in TMS evoked potentials, with some suggesting the use of reduced currents in pediatrics (Moliadze et al., 2015, 2018). This is not evidently based on safety. 2 mA currents have been used in pediatric populations, and the increased sensitivity remains far from levels considered injurious.

In 2018, Meiron et al (Meiron et al., 2018, p. 20), successfully applied 10 sessions of 4x1 HD-tDCS (intensities up to 1 mA) in a case report of a 30-month-old child suffering from early onset epileptic encephalopathy. There were no SAEs or SEs related to the HD-tDCS intervention. Battist et al (2025) extensively evaluated the tolerability, safety, and blinding of tDCS and tRNS in paediatric clinical populations, composed of 92 children and adolescents (54 females, age range: 8-17 years), involving 1032 sessions across neuropsychiatric (i.e., anorexia nervosa) and neurodevelopmental (i.e., attention deficit and hyperactivity disorder, developmental dyscalculia) conditions. It compared AEs occurrence between active and sham tES conditions (i.e., 528 active vs. 504 sham sessions) as well as tDCS and tRNS (i.e., 772 tDCS sessions vs. 260 tRNS sessions), while considering demographic and emotional-behavioural factors. Results demonstrate the safety of tES, with no moderate or severe AEs reported. Approximately 77% of sessions were free of any AEs, supporting the use of tES in these populations. Although active sessions showed a higher likelihood of AEs compared to sham, these events were predominantly mild, mostly limited to itching, indicating a generally benign safety profile. However, the study did not assess the effect of AEs occurrence separately for tDCS and tRNS.

In 2020, Splittberger et al. (2020) reported the case of a healthy 13-year-old girl who experienced her first generalized tonic-clonic seizure within a week after undergoing a single tDCS session. In the present observation, no direct causal relationship between the tDCS and the seizure can be established, especially since the seizure occurred five days after stimulation. Rather, this case highlights that

previously undiagnosed conditions can emerge by chance and underscores the need to take appropriate measures to minimize such risks as much as possible.

Conclusions and recommendations: Studies conducted in pediatric populations have not reported a significantly higher incidence of AEs compared to those observed in adults. In terms of tolerability, there are no major concerns regarding the use of tES in pediatric populations. There is no evidence for long-term aftereffects, including in children; ongoing studies on long-term effects are useful. In research involving children and adolescents, particular attention should be paid to the language used during informed consent and when assessing eligibility. To ensure participant safety, tES studies in this population should implement age-appropriate screening procedures and systematically monitor AEs after each stimulation session. Furthermore, a rigorous ethical framework is needed, including greater transparency and consistent reporting of unusual or unexpected cases (Sierawska et al., 2019, 2020; Splittgerber, Salvador, et al., 2020).

7.4. tES in aging populations

Building upon Antal et al. (2017), we focused on studies published since 2017 that explicitly report SEs or AEs in their title or abstract, selecting those involving healthy (Menassa et al., 2023) older adults (≥ 60 years)(World Health Organization, 2021). While not exhaustive of all NIBS research in this population, our analysis includes both experimental and review studies on tDCS, and tACS. A summary of the selected articles is presented in Table S4.

Consistent with previous findings, most studies continue to use tDCS with a current intensity of 1.5–2 mA and 35 cm² electrodes, targeting the frontal or parietal cortex for 15–30 minutes. Several studies investigated safety outcomes in DLPFC stimulation. Antonenko et al (2022) applied 1 mA tDCS with electrodes of 5cm diameter and found no significant differences in reported sensations between active and sham conditions; similar to Yu et al. (2020) that applied 1.5 mA tDCS with 35 cm² electrodes. Manor et al. (2018) used 2 mA and observed only mild, transient SEs, primarily sensations under the electrode (active: 65%, sham: 70%), skin redness (32% vs. 16%), and sleepiness (30% vs. 14%), and Asseondi et al. (Asseondi et al., 2022), reported only mild AEs over 5 sessions of 2mA with 3.14 cm² electrodes over the DLPFC. Similarly, two studies analyzing data from the "Augmenting Cognitive Training in Older Adults" study (Woods et al., 2018) found that, across 20 sessions of 2 mA tDCS over the bilateral DLPFC, participants reported mild sensations (mostly tingling and burning), with no other AEs (Hausman et al., 2023a, 2024). A higher number of individuals in the active group reported high blood pressure; however, this has not been linked to the effects of stimulation (Hausman et al., 2023a). Self-administered at-home application of 1 mA combined with cognitive training demonstrated not only similar sensations between active and sham conditions, but also excellent feasibility and acceptability (Rocke et al., 2024). Other studies targeted different cortical areas. Dumel et al. (Dumel et al., 2018) applied 2 mA anodal tDCS over the left M1 hand area (42 cm² sponge electrodes) but did not report AEs. Luckey et al. (Luckey et al., 2020) used 1.5 mA tDCS over the C2 dermatomes for 12.5 minutes (35 cm² sponge electrodes), with only mild sensations of itching and tingling and no significant differences between active and sham groups. One study also investigated tDCS safety in older adults (70-90 yrs) with pacemakers, applying 2 mA over the DLPFC with no reported AEs (Roncero et al., 2020).

For HD-tDCS, safety considerations were discussed in three studies, including two reviews analyzing clinical trials in healthy and clinical populations, with partial data overlap (El Jamal et al., 2023; Reckow et al., 2018). These reviews examined SEs across different intensities (2 and 3 mA) and stimulation targets (parietal, temporal, or prefrontal cortex), reporting no unexpected or severe AEs. The most frequently reported sensations were tingling, burning, and itching, occurring in 15–59% of sessions, with most effects rated as mild. Severe sensations were reported in fewer than 4% of cases, and no serious AEs were observed. One experimental study by Lo et al. (2023,(Lo et al., 2023)) investigated HD-tDCS safety in six participants undergoing 1.5 mA anodal stimulation over the DLPFC for 20 minutes. Sensations under the electrodes were reported in 12.1% of sessions, and skin redness in 2.4%, with no severe effects.

For tACS, no studies in older adults are explicitly assessing safety. However, two reviews (Al Qasem et al., 2022; Wu et al., 2024) discussed its use in modulating cognitive functions in healthy older adults

without reporting safety concerns. An ad-hoc search identified 16 tACS studies employing current intensities of up to 2 mA, with stimulation commonly targeting the DLPFC (Diedrich, Kolhoff, Bergmann, et al., 2024; Diedrich, Kolhoff, Chakalov, et al., 2024; Draaisma et al., 2022; Grover et al., 2022; Krebs et al., 2021a), motor cortex (Gamage et al., 2025; Guerra et al., 2021; Rumpf et al., 2019), posterior parietal cortex (Draaisma et al., 2022; Misselhorn et al., 2020), and temporal regions (Reinhart & Nguyen, 2019). These studies utilised a range of frequencies, including theta, alpha, beta, gamma, theta–gamma coupling, and individualized frequency protocols (Draaisma et al., 2022; Fresnoza et al., 2018). Overall, only mild AEs were reported, with no significant differences observed between active and sham stimulation groups. Notably, phosphenes were reported in only three studies (Diedrich, Kolhoff, Chakalov, et al., 2024; Rumpf et al., 2019), and one study using alpha and beta frequency tACS reported ineffective blinding (Rumpf et al., 2019).

In studies employing high-frequency tRNS (100 - 640 Hz) only mild AEs were reported, although one participant dropped out from the active group due to headache (Brambilla et al., 2021). Studies targeted various brain regions, including the dorsolateral prefrontal cortex (DLPFC) and broader prefrontal areas (Brambilla et al., 2021; Maltezou-Papastyliaou et al., 2022), as well as the occipital and fronto-occipital cortex (Esposito et al., 2021; Fertoni et al., 2019).

Conclusions and recommendations: The safety recommendations outlined by Antal et al. (2017) for tDCS remain valid, as no evidence contradicts them. Overall, reported AEs across tES modalities were mild and transient, with no significant differences between active and sham conditions, highlighting the effectiveness of standard sham protocols. However, a lack of use of standardized tools and requirements for AE assessment and reporting remains a limitation, particularly for older adults. Further research is needed, particularly on tACS, and tRNS, and special aging populations such as individuals with pacemakers.

8. Safety for tES as therapeutic intervention

8.1. Note on inclusion and exclusion criteria in therapeutic interventions

The exclusion criteria in therapeutic interventions are generally the same as for healthy people, (see Section 7.1), with the exception of the pathology they are intended to treat. For example, tES interventions for epilepsy will have all exclusion and inclusion criteria as studies in healthy people, but they will include (not exclude) people with a history of epilepsy or epileptic seizures. Furthermore, the possible add-on effects of different kinds of medications should also be considered.

8.2. Psychiatric conditions

8.2.1. tDCS in major depressive disorder and bipolar depression.

In major depressive disorder (MDD), large randomized trials applying 2 mA over the DLPFC for 20–30 minutes per session have reported excellent tolerability, with AEs limited to transient scalp discomfort and no serious AE (Brunoni et al., 2011, 2012). Treatment-emergent mania or hypomania is exceedingly rare, with isolated case reports in bipolar II patients (Chao et al., 2018; Gálvez et al., 2011) and systematic reviews indicating incidence rates below 1%, comparable to those seen with pharmacotherapy (Dondé et al., 2018). No patients have been reported to discontinue tDCS due to adverse psychiatric or neurological symptoms, underscoring its safety in mood disorders. These findings are reinforced by two recent studies demonstrating the feasibility and safety of at-home tDCS for major depression. In an observational cohort, Charvet et al. (2023) showed significant symptom reductions by week 2 of a 6-week home-based protocol, with continued improvement during a taper phase (Charvet, Harrison, et al., 2023). In a large, fully remote, multisite randomized controlled trial, Woodham et al. (2025) further demonstrated the efficacy and acceptability of 10 weeks of home-based tDCS, with greater reductions in depressive symptoms compared to sham and no differences in discontinuation rates and no induced manic/hypomanic states (Woodham et al., 2025).

8.2.2. tDCS in schizophrenia

tDCS protocols targeting hallucinations, negative symptoms or cognitive deficits in schizophrenia also reveal no safety issues. In childhood-onset schizophrenia, bilateral 2 mA tDCS over the DLPFC and superior temporal gyrus was well tolerated with no serious AEs in 10 sessions (Mattai et al., 2011). Similarly, the STARTS randomized clinical trial of 100 adults with predominant negative symptoms found

no significant difference in overall AE rates between active and sham groups (10 sessions, 2 per day), aside from a higher rate of a mild scalp burning sensation in the active arm (active 43.8% vs sham 14.3%) and no participants withdrew due to AEs (Valiengo et al., 2020). A recent meta-analysis compiling data from multiple randomized controlled trials (RCTs) reported that tDCS using the same electrode montage was safely administered to over 320 patients with treatment-resistant auditory hallucinations, without any reported serious AEs, no exacerbation of positive psychotic symptoms, and no discontinuation (Jiang et al., 2022).

8.2.3. tDCS in other psychiatric conditions

In drug-resistant obsessive compulsive disorder (OCD), add-on tDCS trials have reported only mild, self-limited itching, tingling, and transient headache, without serious AEs or treatment discontinuations ((da Silva et al., 2019), for both once- and twice-daily sessions: (Bation et al., 2019)).

In posttraumatic stress disorder (PTSD), 10 sessions of tDCS (2 mA) delivered over the DLPFC documented no serious AE, with mild AEs confined to brief scalp sensations and transient headaches (Ahmadzadeh et al., 2019)

In anorexia nervosa, a double-blind, sham-controlled tDCS trial in 43 inpatients reported no serious device-related AEs; AE rates were comparable between active and sham groups, with two withdrawals due to headache and one transient mood elevation suggestive of hypomania (Baumann et al., 2021).

8.2.4. tACS in psychiatric conditions

A limited number of controlled trials have investigated the efficacy of tACS in psychiatric conditions (Frohlich & Riddle, 2021; Gholamali Nezhad et al., 2024; Perera et al., 2023). In this study population, additional awareness about potential risks is required, including elevated baseline suicide rates when compared to healthy populations without psychiatric conditions. Three RCTs have examined tACS for depression. Two of them used a proprietary waveform that the authors refer to as tACS despite both the waveform and montage differs from tACS. An RCT of this stimulation paradigm in the first depressive episode in MDD(20 daily sessions, 40 min,77.5 Hz,15 mA) reported tinnitus, discomfort, headache and itches as the most frequent AEs with no statistically significant difference between groups (Wang et al., 2022). No serious AEs occurred, and importantly, no transitions to (hypo-)manic symptoms or suicide attempts were reported. The same stimulation paradigm was then studied in patients who were receiving SSRI medication treatment (Zhou et al., 2024). Similarly, no serious AEs and no statistically significant difference in AEs (headaches, drowsiness, dizziness) was reported. An RCT of alpha- and gamma-frequency tACS demonstrated safety for lower frequency stimulation that directly targets cortical oscillations associated with depression symptoms (Alexander et al., 2019). This study reported worsening of suicidal ideation in four participants, all of which were in the sham group. No participant developed (hypo-)mania and no suicide attempt occurred in the study. The only stimulation experience that differed between groups was phosphenes, which do not represent a safety concern but rather a nuisance for effective study blinding. Together, these studies support the safety of tACS in depression. RCTs of tACS in psychotic disorders (Chang et al., 2021; Mellin et al., 2018; Zhang et al., 2022) further support this conclusion. An additional study investigated the use of individualized alpha tACS in OCD (Perera et al., 2023). No SAEs were reported, and only minor infrequent SEs and AEs (headache, tingling, phosphenes, itching). Overall, the current literature supports the safety of tACS in psychiatric populations given the lack of serious AEs and no statistically significant differences in stimulation-associated sensory perception and SEs. However, the heterogeneity of stimulation protocols and study populations together with the small sample size make general conclusions challenging.

Conclusions and recommendations: Overall, evidence across a broad spectrum of psychiatric conditions attests to a favorable safety and tolerability profile of tDCS, characterized by only mild, transient AEs and an absence of serious or lasting adverse outcomes. Regarding tACS, none of the studies reported any serious AEs. Furthermore, most stimulation related SEs were not statistically different between active and sham groups. Of particular relevance, no attempted or completed suicide attempts have been reported in any of the published tACS trials in psychiatric disorders. Together, the current literature supports the safety of tACS in psychiatric disorders. Nevertheless, given the vulnerability of this population, assessment of suicide risk at enrollment together with monitoring of changes to suicide risk throughout the study are recommended.

8.3. Chronic pain and migraine

There is evidence demonstrating the general tolerability, favorable safety profile, and low incidence of AEs in individuals with chronic pain or migraine. The most commonly reported SEs and AEs are: (i) mild and transient sensory disturbances at the site of stimulation, including itching, tingling, burning sensations, or light headaches; (ii) general symptoms, including sleepiness, fatigue, dizziness, nausea, mood change and trouble to concentrate; (iii) local AEs, such as skin redness (erythema) (Ahdab et al., 2019; Hervik et al., 2024; Jobin et al., 2025; Mendes et al., 2024). In sham-controlled studies, the occurrence of such SEs and AEs, except for local erythema under the electrodes, did not differ between the active and sham conditions (Alwardat et al., 2020; Cerrahoğlu Şirin et al., 2021; Hong et al., 2022). However, it remains essential to implement systematic monitoring and documentation of AEs throughout the intervention period to ensure participant safety.

Notably, no serious AEs of tDCS treatment have been reported across a range of clinical populations, including individuals with fibromyalgia (Yang et al., 2024), chronic low back pain (Alwardat et al., 2020), spinal cord injury (Portaro et al., 2025), chronic cancer pain (Grenouillet et al., 2025), episodic migraine (Ahdab et al., 2019; Hong et al., 2022), abdominal pain (Bayer et al., 2019), chronic headache (Hervik et al., 2024), and comorbid psychiatric conditions such as depression, anxiety (Wen et al., 2022), and bipolar disorder (Mastria et al., 2021). These findings support the safe application of tDCS in both clinical and investigational contexts in the pain domain.

Home-based tDCS has also been explored for chronic pain treatment and appears to be generally safe, well-tolerated, and feasible for self-administration (Antonioni et al., 2024). This is further supported by a pilot randomized controlled trial in veterans with persistent post-traumatic headache, where 20 sessions of home-based, remotely supervised tDCS significantly reduced moderate-to-severe headache days and total headache days, with high adherence and no significant safety concerns reported (Charvet et al., 2023). In one study of 12 patients with chronic pain syndrome treated by tDCS at home for several weeks (Garcia-Larrea et al., 2019), AEs were further detailed: two patients experienced acute AEs, including nausea, headache, or digestive disorders. It was concluded that these events were unrelated to the tDCS procedure. The treatment was not interrupted and was effective in reducing pain; two other patients reported superficial skin burns beneath the electrodes due to incorrect electrode application. This led to changing the type of electrodes (from Ag/AgCl electrodes of 3.14 cm² contact area to larger sponge electrodes of 8 cm² contact area) without further problems for the rest of the treatment.

tACS has been proposed to restore pathologically altered rhythmic brain activity associated with pain. There are only a few tACS trials performed in chronic pain patients, in the context of migraine (Antal et al., 2020) or chronic low-back pain (Ahdab et al., 2019; Ahn et al., 2019; Prim et al., 2019). Neither study reported any serious AEs. For the migraine study (Antal et al., 2020), tACS was performed at home (single session, 15 min at 0.4mA at 140Hz, Oz-Cz montage) and a few participants reported pain under electrodes, tingling, itching, nervousness, fatigue, and unpleasantness. However, the occurrence rate was low and no statistically significant differences were reported compared to sham procedure. Similarly, a single session of alpha-frequency tACS (20 minutes at 1 mA, 10 Hz) applied in a cross-over design with an active sham comparator in individuals with chronic low back pain was not associated with a statistically significant difference in stimulation-related SEs (Ahn et al., 2019; Prim et al., 2019). Overall, tACS appears well tolerated and safe. However, the small number of studies and the low number of participants do not allow for any strong conclusions. However, it is noteworthy that, in a sham-controlled study on patients with fibromyalgia, one patient in the active group attempted suicide by overdose. In this study, an unusual theta-burst protocol was delivered (monophasic square wave with a pulse width of 0.5 ms and intensity of 1 mA at 50 Hz, repeated at duty cycle with on time of 2 s and off time of at 1 mA). The psychiatric history of the patient was not provided, and caution is advised in determining whether this event was causally related to the study intervention. In any case, it is recommended that in participants with complex medical or psychiatric histories, a suicide risk screening is included in the study protocol.

Recommendation: While no significant risks have been identified for the use of tDCS to treat chronic pain, even for several weeks at home, the long-term safety of extended tDCS use remains to be investigated to refine safety protocols for prolonged therapeutic use. Regarding tACS, it appears well

tolerated and safe. However, the small number of studies and the low number of participants do not allow for any strong conclusions

8.4. Stroke neurorehabilitation

tDCS has been applied in stroke rehabilitation across 177 published studies, involving a total of 6,509 patients. Depending on the rehabilitation target, tDCS targeted the ipsi- or contralesional motor cortex in most studies, but also other areas such as nodes of the fronto-parietal language network. Stimulation intensities typically ranged between 1–2 mA, though safe administration at intensities up to 4.0 mA has been reported (Chhatbar et al., 2017; Schlaug et al., 2025). The typical session duration in stroke recovery trials ranged from 20 to 30 min, with some extending up to 40 min. tDCS was well-tolerated, and AEs were both mild and transient. The most commonly reported AEs during active stimulation included tingling (n = 108 vs. 45 for sham), itching (n = 56 vs. 34), skin redness (n = 36 vs. 8), headache (n = 17 vs. 9), mild burning (n = 16 vs. 11), and fatigue (n = 16 vs. 2). Serious AEs, such as stroke, myocardial infarction, or death, were rare and occurred at similar rates in both the active (n = 12) and sham (n = 13) groups. Notably, the study authors consistently judged these serious events to be unrelated to the tDCS intervention and more likely attributable to the patients' pre-existing medical conditions. Home use of tDCS has also been validated for patients recovering from aphasia (Richardson et al., 2023).

tDCS in the hyperacute phase of stroke has been less well studied. The first two RCTs applying conventional tDCS and HD-tDCS in hyperacute stroke were conducted in France (STICA) and the USA (TESSERACT), (Bahr-Hosseini & Bikson, 2021; Pruvost-Robieux et al., 2021). These pilot studies were underpowered for efficacy evaluation. However, the results suggested a benefit upon penumbral salvage. The stimulation was safe and well tolerated in emergency settings.

Anodal tDCS was applied to the swallowing sensorimotor cortex or the pharyngeal motor cortex to improve swallowing in patients with post-stroke dysphagia, showing a strong safety profile. In an RCT with 42 patients receiving either up to two daily 20-min sessions of anodal tDCS targeting the unaffected swallowing motor cortex at 2 mA for 10 days or sham tDCS, no decline in global neurological, motor or swallowing functions or seizures were reported in any of the intervention arms (Kumar et al., 2022). Unanticipated serious AEs reported were adjudged as not being related to the stimulation (see Section 13.1 for details). Anodal tDCS of the contralesional swallowing sensorimotor cortex at 1.6 mA for 20 min daily for 6 days over 8 weeks in patients with brainstem stroke was without any AEs (Mao et al., 2022). No AEs were also reported in other trials with dysphagic stroke patients applying either four anodal tDCS of the contralesional swallowing motor cortex 20-min sessions at 1 mA (Suntrup-Krueger et al., 2018) or bilateral anodal tDCS of the pharyngeal motor cortices at 1 mA for 20 min daily for 10 days (Ahn et al., 2017)

tACS was reported in 11 studies involving 156 subacute or chronic stroke patients that were treated with a broad variety of tACS protocols. Protocols varied widely in intensity (0.4–3.0 mA), frequency (6–120 Hz), and session duration (up to 120 minutes), with treatment plans including up to 20 sessions. Only 5 articles reported on perceptual SEs, AEs and/or tolerability (Grigutsch et al., 2024; Kitatani et al., 2020; Middag-van Spanje et al., 2024; Omae et al., 2024; Schuhmann et al., 2022). No SEs or AEs were noted, and tolerability was high. Five patients discontinued study participation, four with reasons not related to the tACS intervention, and one due to a mismatch of expectations with the therapeutic program.

tRNS has demonstrated a favorable safety profile in stroke, with SEs predominantly mild and transient. Current evidence indicates that tRNS applied at 2 mA (100–500 Hz) for 30 min is generally associated with minimal sensations such as tingling (Sethi et al., 2023). When combined with movement-triggered stimulation (Hayward et al., 2017) or integrated into motor rehabilitation programs such as the graded repetitive arm supplementary program (Arnao et al., 2019), tRNS has not been associated with AEs. Across the three published studies (n = 19 patients treated with tRNS), no serious AEs have been reported, and participant adherence has been consistently very high, with no dropouts observed.

Recommendation: While there is no evidence of serious AEs associated with tDCS, tACS, and tRNS in stroke patients, ongoing monitoring for mild AEs is recommended. Adjustment of stimulation parameters (intensity, duration, electrode montage) may further improve comfort and tolerability. The integration of tDCS, tACS or tRNS with adjunctive therapies (e.g., functional electrical stimulation or motor training) appears feasible and well tolerated, though standardization and individualization of

protocols are recommended to ensure safety and optimize outcomes. The safety evidence is strongest for tDCS, with over 6,500 stroke patients studied. In contrast, evidence for tACS and tRNS remains limited, highlighting the need for larger, well-controlled trials.

8.5. Multiple sclerosis (MS)

tDCS has been extensively studied for its safety and tolerability in individuals with multiple sclerosis (MS), particularly as a home-based intervention delivered through remotely supervised tDCS (RS-tDCS). Fatigue was among the earliest symptoms targeted, as this debilitating condition lacks consistently effective treatments in MS. In an initial randomized, sham-controlled trial using home-based RS-tDCS targeting the left DLPFC, 20 sessions were well-tolerated and associated with reductions in fatigue (Charvet et al., 2018). A subsequent larger multisite trial confirmed the safety and feasibility of the same protocol (Charvet et al., 2025a). There were no serious AEs, across all participants in both conditions, 9 AEs were rated > 7 on the VAS; in all instances, the session resumed. One participant discontinued one session due to discomfort at the stimulation midway check-in point. Otherwise, all AEs were reported as mild in intensity and resolved after the session ended. Concerning feasibility, in the 117 individuals randomized, an average of 26 ± 9 sessions were completed; only four patients withdrew before completing any sessions and seven withdrew who completed fewer than 10 sessions. Attrition remained minimal, demonstrating a high level of fidelity to treatment, with 92.0% of participants completing at least 25 of the 30 sessions by the end of treatment.

Importantly, tDCS has demonstrated a favorable safety profile in individuals with MS over extended treatment intervals (Pilloni et al., 2022). Two systematic reviews report that adverse events such as headache, insomnia, and mild sensory symptoms occurred at similar rates between active and sham stimulation, with no SAEs reported (Ashrafi et al., 2020). Applications of RS-tDCS for cognitive symptoms have also consistently demonstrated strong safety and tolerability. Multiple randomized trials have shown no SAEs while reporting benefits in complex attention, response variability, and overall cognitive performance, particularly in participants with greater baseline disability (L. Charvet et al., 2018, 2025b; Riemann et al., 2025). Applications for motor symptoms have been similarly well-tolerated. A trial combining 10 sessions of M1-targeted tDCS (2.5 mA) with aerobic exercise demonstrated excellent tolerability along with improved gait speed and endurance (Pilloni, Choi, Coghe, et al., 2020). Only perceptual effects of itching, tingling, and head pain were reported with no higher intensity level of >7 (rated on a 0- to 10-point scale) for any participant, and all of them were resolved at the end of the stimulation period. In progressive MS, home-based RS-tDCS paired with dexterity training over 20 sessions showed positive outcomes in hand function and quality of life, with no serious safety concerns (Pilloni et al., 2024). 1077 at-home RS-tDCS sessions were completed, no session was discontinued due to tolerability, and only during six sessions ($n = 3$ active and $n = 3$ sham tDCS sessions) did participants report discomfort > 7 on the VAS. Only one participant reported itching with an intensity higher than 7 in two separate sessions. In all cases, all participants opted to continue treatment and the session was resumed without further tolerability issues. Across sessions, tingling was the most frequently reported sensation (reported by 30% active versus 35% sham participants) followed by itching (reported by 18% vs 7%) and warmth sensations (reported by 15% vs 8%). tDCS has also been explored for comorbid behavioral conditions. In a randomized trial of women with MS and cannabis use disorder, RS-tDCS paired with mindfulness meditation was safely administered and associated with reduced cannabis use, decreased withdrawal symptoms, and improved cognitive function (Pilloni et al., 2025). 45 participants initiated the intervention ($n = 30$ active tDCS, $n = 15$ sham tDCS), with 83 % completing at least 14 of the 20 planned sessions. There were no dropouts related to the intervention, the most commonly reported sensations during the sessions were tingling, itching, and warmth, in agreement with our previous reports.

Beyond tDCS, other noninvasive stimulation modalities have also been evaluated in MS. A study of bifrontal 6 Hz tACS reported only mild to moderate AEs across 180 sessions, with no differences between active and sham groups, and notably, no phosphenes reported by any participant (Hsu et al., 2023).

Similarly, tRNS was studied for effects on affect, pain, and attention; side effects such as insomnia, nausea, and headache occurred at comparable rates in active and sham groups, and only one sham-treated participant reported phosphenes (Palm et al., 2018). Discomfort ratings did not differ by stimulation condition, further supporting the tolerability of these interventions.

8.6. Dementia and mild cognitive impairment (MCI)

A network meta-analysis of randomised controlled trials on the beneficial effects of NIBS on cognition in dementia (Tseng et al., 2023), which included 7 tDCS studies, found that none of the NIBS methods were associated with different rates of any AEs compared with sham controls. A study of 11 patients with mild cognitive impairment (MCI), who received 2mA tDCS for 20 minutes per day over 5 consecutive days (55 sessions in total), reported a pricking sensation (n = 30, 55%) and a mild burning sensation (n = 8, 14%) as the most common AEs; no AE was reported in 15 sessions (31%), while all reported AEs were of mild intensity (Murugaraja et al., 2017). Another study that assessed 46 patients with subjective or objective cognitive impairment after 9 sessions of combined cognitive training with either anodal tDCS (1 mA) or sham tDCS over the DLPFC found 15 AEs in 4 participants in the target group, and 16 AEs in 7 participants in the control group, without significant difference between groups; no SAEs occurred in this study (Antonenko et al., 2024). In terms of efficacy, no significant difference emerged in the primary outcome measure of trained task performance in the letter updating task, but a significant difference was found for the N-back working memory tasks (secondary outcome). In individuals with both MCI and depression, a six-week randomized sham-controlled trial demonstrated that prefrontal tDCS was 'well tolerated' and associated with electrophysiological markers of enhanced neuroplasticity, although behavioral improvements did not reach significance (Kim et al., 2024). In the paper no AEs or perceptual effects of the stimulation are reported. A larger multisite randomized clinical trial combining prefrontal tDCS with cognitive remediation in older adults with MCI and/or remitted major depressive disorder (rMDD) also confirmed the safety and acceptability of the protocol. While cognitive outcomes varied by APOE ϵ 4 status and depression history, no serious AEs were reported (Martin et al., 2019). There were no significant differences between conditions in the frequency of the following reported AEs: redness, tingling, mild burning, pain, nausea, light headedness, headache, blurred vision, fatigue. For the ITT sample, the most common AEs reported across all sessions were: tingling (25.9%), redness (16.2%), mild burning (11%), and itching (10.5%). Another trial similarly confirmed the feasibility and tolerability of tDCS delivered with cognitive training, although it did not find an additive cognitive benefit over sham (Hausman et al., 2023b). Throughout the trial, the sham group reported more body-related AEs, while the active group reported more cardiac-related adverse events. In particular, there was a greater number of individuals reporting high blood pressure in the active group (15 in the active vs 6 in the sham group), which has not been shown to be related to effects of stimulation. In the domain of language disorders, a recent study in individuals with primary progressive aphasia found that home-based RS-tDCS paired with speech-language therapy was feasible, well tolerated, (George et al., 2025). In this observational study only 10 patients participated. All participants successfully completed all scheduled intervention sessions, resulting in a 100% completion rate.. Consistent with prior studies, there were no serious AEs reported during the intervention. Mild, self-limited sensations such as tingling at the electrode site were reported by two participants but did not disrupt adherence or require further intervention. **Conclusions:** No specific safety concerns related to tES are detected specific to this patient group.

8.7. Amyotrophic lateral sclerosis (ALS)

A recent study of home-based tDCS in amyotrophic lateral sclerosis (ALS)(Madhavan et al., 2025b), following 72 tele-tDCS sessions over 24 weeks in 16 patients, reported only usual mild to moderate AEs (with itching and tingling being the most pronounced), without significant difference between the intervention and delayed-onset (control) groups. **Conclusions:** No specific safety concerns related to tES are detected specific to this patient group.

8.8. Parkinson's disease (PD)

No AEs were reported in studies including patients with Parkinson's disease (PD), as shown in a network meta-analysis (Qiu et al., 2023). Moreover, RS- tDCS has been found feasible for home use in PD, yielding benefits in fatigue and cognitive processing speed with high tolerability; tingling (43%) and burning sensation (29%) were common but represent mild AEs (Dobbs et al., 2018). Regarding cerebellar tDCS, in a meta-analysis including 12 studies on movement disorders, one reported local skin erythema, five reported no AEs, but the other six did not mention relevant information (França et al., 2018). Other tES methods have been tested as a treatment for PD as well. Two studies, based on gamma-frequency tACS (Guerra et al., 2022) or tRNS (Monastero et al., 2020) delivered over M1 did not report significant safety concerns. **Conclusions:** No specific safety concerns related to tES are detected specific to this patient group.

8.9. Epilepsy

Low-intensity tES was used in patients with epilepsy for various purposes, much of it using cathodal tDCS. Across all these use cases, there is no evidence of an increased safety risk to epileptic patients (Bikson et al., 2016; Nitsche & Paulus, 2009; Simula et al., 2022; Sudbrack-Oliveira et al., 2021). However, the available evidence remains limited, and while hyper-excitabile brain networks may respond differently to electric fields, this does not constitute evidence of a safety risk. The common exclusion of history of seizures from tES protocols is based on precautions using rTMS. **Conclusions:** No specific safety concerns related to tES are detected specific to this patient group.

8.10. Other clinical conditions

8.10.1. Viral infections

In patients with Human Immunodeficiency Virus (HIV), 10 HD-tDCS sessions targeting the cingulate cortices at 1.5 mA over two to three weeks to improve brain function was well-tolerated, with no significant difference in self-reported discomfort ratings between sham and active conditions (Jiang et al., 2022). Ten 20-min sessions of anodal tDCS of the right inferior frontal cortex at 2 mA combined with cognitive training to improve cognitive functioning in 33 older adults with HIV did not lead to any AEs (Fazeli et al., 2019). Cody et al. (2020) tested the same protocol as Fazeli et al. (2019) comparing its impact on sleep quality and processing speed in the elderly with versus without HIV. One participant reported a burning sensation similar to a sunburn during the stimulation and the tDCS intensity was reduced to a level she could tolerate. Nevertheless, it was not specified whether the participant was in the HIV or non-HIV sample.

The safety profile of tDCS was also explored in different subgroups of COVID-19 patients. The combination of HD-tDCS targeting the left diaphragmatic M1 (twice per day at 3 mA for 30 min) and respiratory rehabilitation for up to 10 days in 56 critically ill patients was well-tolerated and safe, with similar patterns in AEs in both sham and active groups (Andrade et al., 2022). The only AE associated with active tDCS was mild and transient redness of the scalp. In a recent trial testing the effects of 10 sessions of HD-tDCS of the left M1 at 3 mA for 20 minutes paired with rehabilitation on fatigue in 70 patients with post-acute sequelae of COVID-19, the occurrence of no other AEs, except skin redness, differed significantly between sham and active arms (Santana et al., 2023, p. 20). In addition, no serious AEs were reported in this study. A single session of bilateral prefrontal tDCS over the DLPFC at 2 mA for 30 min in 40 COVID-19 inpatients was safe, with no serious AEs for any patient up to 1 h post intervention and no differences in occurrence and intensity of AEs between sham and active groups (Pinto et al., 2023). Headaches and sleepiness were the most frequently reported consequences in the sham group while tingling was the most reported SE in the active group.

Currently, a large multi-center trial is evaluating a 50-session RS-tDCS protocol paired with cognitive training to treat cognitive impairment in individuals with post-acute sequelae of SARS-CoV-2 infection (Knopman et al., 2024).

8.10.2. Cancer

In a recent scoping review by Capetti et al. (2024) including 10 trials testing the effects of tDCS in the reduction of pain and psychocognitive symptoms in cancer patients, only Gaynor et al. (2020) reported AEs. Two sessions of anodal tDCS at 1 mA over the left DLPFC in an F3-F4 montage to improve sustained attention in 16 breast cancer survivors was well-tolerated, with burning sensation on the scalp and itching being the most frequent AEs rated as mild or moderate. No sessions needed to be stopped because of AEs (Gaynor et al., 2020).

8.10.3. Obesity

tDCS protocols targeting weight loss in obesity demonstrated a favorable safety profile in patients with obesity. A systematic review including 7 randomized clinical trials with 170 patients using mainly anodal tDCS of the DLPFC (unilateral or bilateral) at 2 mA for a duration of 20 to 40 min documented no severe AEs (Gouveia et al., 2021). Only transient mild AEs including headache, neck and scalp pain, scalp burn, and skin redness were reported in both active and sham intervention groups.

8.10.4. Type 1 diabetes mellitus

In type 1 diabetes mellitus, one 20-min session of HD-tDCS targeting the bilateral DLPFCs with total current delivered of 1.5 mA for improving performance in cyclists was well-tolerated and no SE or AE was reported during or after the stimulation (Filipas et al., 2022).

8.10.5. Systemic lupus erythematosus

Only one study investigated the impact of tDCS in patients with systemic lupus erythematosus (de Andrade et al., 2024). The combination of five sessions of anodal tDCS over the M1 at 2 mA and low-intensity aerobic exercise was well tolerated, with the presence of only mild and transient AEs and the absence of any disease flares.

8.10.6. End-stage renal disease

The safety of 10 20-min daily sessions of anodal tDCS of the M1 at 2 mA in 30 patients with end-stage renal disease undergoing hemodialysis was evaluated in an exploratory study through monitoring the participants' tolerance and subjective sensations to the stimulation (Pegado et al., 2024). Commonly reported SEs and AEs were headache, nausea and tingling, with no serious AE. The stimulation was well tolerated by the participants.

8.10.7. Tinnitus

A variety of tDCS, tACS, tRNS protocols have all been investigated for the treatment of tinnitus (J.-J. Chen et al., 2020). When AEs were reported, there were either no AEs in either group or transient events such as tingling, dizziness, headaches, facial numbness, itching, scalp pain, burning, pinching, fatigue, headaches or skin irritation which were typically observed in both active and sham stimulation groups (Kreuzer et al., 2019; Pal et al., 2015; Smeele et al., 2023; T. Yang et al., 2021). None of the investigated tES protocols were associated with significantly different dropout rates when compared with the sham control (J.-J. Chen et al., 2020). Occasionally, transient increases in tinnitus were reported, sometimes resulting in patients dropping out of the studies. However, these increases ceased spontaneously. No SAEs have been reported in any study.

Conclusions: This section reviews the safety of tES in less commonly studied disorders, mainly focusing on tDCS. No specific safety concerns were identified for these clinical indications. However, many trials did not assess SE/AE, thus more comprehensive data recording is needed.

9. Combining tES with other methods and interventions

9.1. tES combined with MRI /fMRI

Low-intensity tES during MRI has become a well-established protocol for functional MRI and MR spectroscopy investigating tES-induced brain effects, and electrical tissue property imaging. The first edition of the “Safety, Ethical, Legal, Regulatory, and Application Guidelines,” published in 2017, included a dedicated chapter addressing tES during MRI (Antal et al., 2017b). It concluded that low-intensity tES can be safely used during MRI if specific precautions are strictly followed. This section synthesizes three new studies that specifically addressed safety aspects of concurrent tES-MRI applications and concludes with an updated version of the original recommendations from 2017.

During MR scanning, the TES electrodes and leads inside the scanner bore are exposed to strong radiofrequency (RF) excitation fields (reaching 10-30 kW), requiring special safety considerations to prevent ohmic heating and skin burns. Heating due to low-frequency currents induced by MR gradient switching is usually not of concern. A dedicated tES-MRI safety study has evaluated a new setup for low-intensity tES during MRI using low-conductivity silicon rubber leads to reduce RF coupling and heating (Gregersen et al., 2021). If MRI-compatible tES stimulators use highly conductive copper leads ($\sigma = 5.8 \times 10^7$ S/m), 5 k Ω resistors are added to avoid antenna effects in the copper wire at $\frac{1}{4}$ RF wavelength. High RF electric fields may occur near the safety resistors, so they should be well-separated from the skin. To reduce RF-induced heating and antenna effects, leads with distributed resistance and lower total impedance are preferred. Carbon fiber leads, common in EEG-MRI, lower SAR compared to copper. For tES-fMRI applications, even safer performance is achieved using low conductivity silicone rubber leads ($\sigma = 29.4$ S/m). Simulations and temperature tests confirmed improved safety, minimal SAR increase, and no overheating. At the same time, the ohmic resistance of the silicone rubber leads could be kept below 5 k Ω , enabling higher tES current intensities compared to copper leads with added safety resistors. A simulation study developed a workflow to assess RF-induced heating during MRI with a TES setup, showing that temperature rise is highly sensitive to skin conductivity, electrode and gel geometry, and phantom materials. These findings underscore the importance of precise modeling and setup design to ensure accurate safety evaluations and prevent overheating risks during combined tES-MRI procedures (Kozlov et al., 2020).

More than 100 peer-reviewed studies have used low-intensity tES concurrently during MR scanning for functional MRI, MR-spectroscopy, or electrical tissue property imaging. These studies have not reported severe AEs, but explicit reporting of AEs is poor in the existing literature. To address this issue, a checklist for assessing the methodological quality of concurrent tES-fMRI studies, the ContES checklist, has been developed through expert consensus using a delphi procedure (Ekhtiari et al., 2022). In addition to key methodological and technological factors such as electrode setup and stimulation parameters, key safety-relevant factors were identified and grouped as a separate category of items. These items emphasize the need to report MR conditionality of the tES setup, results of safety and artifact testing, any participant intolerance, and impedance measurements to ensure safe and interpretable tES-fMRI integration. Reporting these items was considered to be extremely or highly important. This contrasts with a relatively low reporting rate of approximately 30% for most items that emerged when three independent raters evaluated 57 concurrent tES-fMRI studies. Reporting rate of MR conditionality specifications, such as safety tests for tES-fMRI setting or safety was very low (5%) in these 57 studies, and thus standardized reporting of presence and absence of safety aspects, including AEs, is needed in future tES-MRI studies.

Conclusions and recommendations: Specific safety precautions apply for concurrent tES-MRI. The study protocol must always comply with the safety standards for both tES and MRI. The stimulator (containing ferromagnetic parts) must remain outside the MR room, and the use of MR-compatible cables, electrodes and electrode leads is strictly required. The use of RF filters is strongly encouraged to prevent noise interference on the MR data. Filters are also effective in preventing the cables transmit RF energy of the MR scanner to the stimulator. The electrode leads close to and inside the scanner bore must be arranged without loops and their path lengths inside the bore should be kept as short as possible. Low conductivity silicone rubber electrodes in conjunction with a thick conductive paste are recommended to minimize the risk of burns during prolonged imaging sessions. Saline-soaked sponges are contraindicated due to their tendency to desiccate during extended scans. MR conditionality of tES equipment refers to specific application scenarios (such as scanner field strengths, MR sequences and

sequence parameters) approved by the manufacturer. Concurrent tES-MRI studies outside these scenarios require additional clearance by the manufacturer and/or safety evaluations by qualified MR experts.

9.2. tES simultaneously combined with TMS/rTMS/TBS/ECT

Since 2017, there have been only a few clinical trials in which some form of tES has been applied simultaneously with plasticity-inducing forms of rTMS or theta burst stimulation (TBS) for therapeutic purposes: tDCS with rTMS in moderate Alzheimer's Disease (Hu et al., 2022), or tDCS with TBS in MDD (Wivatvongvana et al., 2024), without noting any AEs. In addition, the concomitant use of tDCS over the DLPFC (anode left/cathode right, 2 mA, 30 min), followed by ultrabrief right unilateral electroconvulsive therapy (ECT) administered 5 to 10 minutes later, appears to be both feasible and safe ((Mayur et al., 2018).

tACS at different frequencies has been used in combination with TBS to investigate physiological effects of brain stimulation, including plasticity, in healthy subjects, without noting any AEs (Guerra et al., 2018; Maiella et al., 2022; Nakazono et al., 2021; Ogata et al., 2021; Takahashi et al., 2024; Tremblay et al., 2017).

All the remaining studies were performed in healthy subjects, again for physiological purposes, mainly in order to study relationships between the effects of EEG activity, tACS frequencies and TMS pulse(s) on cortical excitability, either when TMS pulse was phase-locked or not with the underlying oscillatory EEG activity or with the applied tACS (Fehér et al., 2017, 2022; Feurra et al., 2019; Geffen et al., 2021; Guerra et al., 2016, 2020; Pozdniakov et al., 2021; Raco et al., 2016, 2017; Schilberg et al., 2018; Shpektor et al., 2017). No AEs were noted.

Conclusions: there is the possibility when tES simultaneously applied with TMS/rTMS/TBS that changes in neuronal excitability produced by electrical polarisation can directly affect the response to TMS. However, there is no evidence that the addition of single pulses of TMS increases the incidence of AEs over that of tDCS alone.

The above findings confirm the conclusion from our previous review (Antal et al., 2017a) that there is currently no evidence that simultaneous tES and TMS, when established protocols are followed, introduces a safety risk. Factors such as tolerability (TMS induction of current in tES wires) or equipment interaction should be considered, but are not known to impact safety.

9.3. tES combined with EEG/MEG

To demonstrate on-line and/or off-line effects of tES, it is desirable to record EEG or MEG during and/or immediately before and after tES experiments. Recording EEG during and/or immediately before and after tES requires having EEG electrodes positioned on the scalp and often connected to an EEG amplifier during the stimulation. While applied current might hypothetically divert into EEG electrodes which might then heat up, this is not in fact expected or observed. The reason is the very high input impedance of modern EEG amplifiers (typically in the range of megaohms - M Ω), thus limiting currents to the range of microamps, which cannot result in relevant heating. In addition, the EEG electrode itself presents an electrochemical impedance. Moreover, even if an EEG amplifier could hypothetically represent a short-circuit at the end of the EEG wires, the tES stimulator, being a constant current source, would still limit its current to the selected strength, thus eliminating any potential for tissue damage. Another hypothetical concern is changes in current flow pattern by the presence of the EEG electrodes on the scalp. However, no heating of EEG electrodes was reported in numerous published tES-EEG studies. Moreover, those studies have not reported AEs other than those seen in tES without additional electrophysiological monitoring (Antal et al., 2008; Helfrich et al., 2014; Zaehle et al., 2010) or tDCS (Antal et al., 2004; Cunillera et al., 2016; Faria et al., 2012; Luft et al., 2014; Mancini et al., 2016; Marshall et al., 2006).

Simultaneously recording MEG during tES experiments poses no risks to the participants, since the MEG sensors do not touch the skin and thus cannot conduct tES currents. Various authors have demonstrated combined MEG/tES studies without safety issues (Neuling et al., 2015; Ruhnau et al., 2016). It should be

mentioned that, meanwhile, even intracranial recordings have been conducted during tES without safety concerns (Guidetti et al., 2022; Y. Huang et al., 2017; Lamoš et al., 2025; Louviot et al., 2022).

When tES is combined with EEG, if a stimulation electrode is short-circuited to another stimulation electrode, current will most likely become ineffective. If a stimulation electrode is short-circuited to an EEG electrode, there will be an exceptionally strong artefact in the EEG. If two EEG electrodes are short-circuited, no EEG signal will be observable. Therefore conductive fluids between electrodes must be prevented to avoid short-circuiting adjacent electrodes. Electrode gel is preferable to saline solution (Fehér & Morishima, 2016).

When EEG is recorded during tES, artefacts contaminate the EEG recordings. Artefacts are not a straightforward safety concern, but a recording loaded with artefacts is useless and conducting it would represent an unnecessary burden to participants in experiments and/or treatment procedures, thus causing ethical concerns. Although no device produced so far is able to simultaneously stimulate and record EEG, using the same electrodes, the development of multichannel stimulation/recording devices has allowed EEG recordings from surrounding electrodes even during the stimulation. To acquire meaningful EEG data that leads to interpretable results, the artefacts of tES need to be avoided, removed or minimized ((Helfrich et al., 2014; Neuling et al., 2015), for a review, see (Kasten et al., 2019)). Some authors, however, were not able to remove the artefacts and claimed that they are inherent to recording EEG during tACS and might be impossible to completely remove (Gebodh et al., 2019; Noury et al., 2016). It should be noted that the artefact of tES can exceed amplitudes of 100 mV and bring some EEG amplifiers into saturation (Fehér & Morishima, 2016). Thus, it is advisable to use EEG amplifiers with 24 bit or more and to set the analog/digital (AD) range to well cover the size of the artefact (von Conta et al., 2022). Importantly, EEG amplifiers already show small non-linearities with the specified AD range, which can result in artifactual EEG oscillations at the frequency of interest due to nonlinear distortion of tACS signals (Kasten et al., 2018). Furthermore, the way the sine wave is generated in the tES device (e.g., for tACS) can be responsible for whether artifacts around the stimulation frequency can be seen in the EEG / MEG. Thus, tES devices that work with a high digital to analog conversion quantization (minimum 16 bit) and high sampling rate (e.g. > 10 kHz) to synthesize a sine wave signal are advantageous here.

Conclusion: In the simultaneous recording of brain activity by either EEG or MEG during/before/after tES, no additional sensations or other AEs, beyond ones generally encountered with tES, have been reported.

9.4. Special considerations for intracranial electrodes and implants

Measurements using intracranial recordings to study the mechanisms of tES in humans have become increasingly popular (Guidetti et al., 2022). Early studies using stereo EEG (sEEG) recordings found that tES produces electric fields up to 0.4 mV/mm per 1mA (Huang et al., 2017; Opitz et al., 2016). No AEs were reported for stimulation intensities 0.5-2mA and tACS frequencies up to 100 Hz. Measured electric field values are in line with predictions from electric field models (Datta, Elwassif, et al., 2009; Miranda et al., 2013; Opitz et al., 2018). Since 2017, various labs have performed intracranial recordings in humans during tES without any reported AEs. Recording modalities involved sEEG(Lafon et al., 2017; Louviot et al., 2022; Shan et al., 2023; Simula et al., 2024; Wang et al., 2022), DBS leads (Chhatbar et al., 2018; Esmaeilpour et al., 2017; Ruhnau et al., 2018) and grid electrodes (Salimpour et al., 2017). Invasive recordings were also performed in an individual with brain lesions without reported AEs (Jiang et al., 2022). A recent computational study suggests that the implants could possibly enhance the tES electric field but the effects stay within a safe range (Karimi et al., 2025). However, direct electric field measurements of AC currents in a phantom next to a DBS lead showed only small effects of the implant (10% reduction) (Lamoš et al., 2025). This is in line with another modeling study which predicts only moderate effects of implants on the EF (Mercadal et al., 2022). Local electric field perturbations can affect the stimulation dose and thus complicate the study of tES mechanisms using invasive recordings. This effect may be amplified by the lower resistance of the burr hole if the transcranial electrode is in close vicinity (Datta et al., 2010).

Recommendation: tES appeared to be safe in subjects with implanted DBS or sEEG electrodes within stimulation parameters typically applied in healthy participants. TES on humans carrying any implants in the brain or in the skull should only be performed in well-supervised and controlled studies. Special

attention is required for adaptive implanted brain stimulation which may sense the electric field artifacts by tES.

9.5. Pharmacological interventions combined with tES

The interaction between tES, particularly tDCS, and pharmacological treatments remains a topic of clinical relevance and ongoing investigation. The 2017 guidelines noted that some pharmacological agents may modulate the effects of tES, potentially enhancing or reducing its efficacy, and raised the possibility of safety concerns when combining the two interventions. Since then, several additional studies have investigated the safety, feasibility, and effectiveness of combined tES and pharmacotherapy, particularly in remote or home-based treatment settings.

Recent evidence, primarily from feasibility studies, pilot trials, and case series, supports the general safety and tolerability of tES in patients receiving stable pharmacotherapy across various clinical populations, including MDD, bipolar depression, Parkinson's disease, multiple sclerosis, fibromyalgia, schizophrenia, and temporal lobe epilepsy. SEs and AEs reported in these studies were predominantly mild and transient, such as tingling, itching, or transient discomfort at the electrode site, with no evidence of increased risk attributable to the pharmacological status of the participants (Cappon et al., 2022; Flynn et al., 2024; Ghazi-Noori et al., 2024; Piloni et al., 2022).

Some studies, including large-scale fully remote randomized controlled trials (RCTs), have provided initial evidence of clinical benefit of at-home tES when administered alongside stable pharmacological regimens (Ruffini et al., 2024; Woodham et al., 2024). Nevertheless, most of these studies did not systematically analyze drug-tES interactions, and participants were often required to maintain stable medication regimens or exclude drugs known to lower seizure threshold (e.g., bupropion, clozapine). Moreover, no study so far has reported data about medications prescribed for unrelated conditions that may nonetheless interact with brain stimulation. For example, beta-blockers, sodium and calcium channel blockers—used in antihypertensive, antiarrhythmic and antiepileptic therapies—can diminish the modulatory effects of tDCS by stabilizing membrane excitability. Though statins, hypoglycemic agents, steroid or hormone therapies have not been studied in this context, their widespread use and their indirect effects on the CNS suggest they could also influence tDCS outcomes. Furthermore, drugs potentially leading to cutaneous AEs, e.g., immunosuppressants and immunomodulators, could change the tolerability profile of tES at the site of stimulation.

However, although long-term follow-up data are sparse, available findings suggest that sustained use of home-based tDCS with pharmacotherapy is feasible and generally well tolerated, provided appropriate training, supervision, and adherence to safety protocols are ensured (Dragon et al., 2024; Lee et al., 2022; Lench et al., 2024).

While the safety profile of combined tES and pharmacotherapy appears reassuring, the clinical rationale for their combination should be carefully considered. Specifically, concurrent use should be pursued primarily when a synergistic or additive therapeutic effect is anticipated. Recent evidence suggests that this may not always be the case: a large multicenter RCT found no additional benefit of adding tDCS to sertraline for MDD compared to sertraline alone (Burkhardt et al., 2023). On the other hand, potential risk associated with tES in depression is treatment-emergent mania (A. R. Brunoni et al., 2017), for which co-administration of mood stabilizers has been recommended to mitigate this risk (Tatti et al., 2022).

Conclusions and recommendations: While no new evidence has emerged that clearly indicates an increased risk or clinically significant adverse interaction between tES and pharmacotherapy, current findings are largely based on feasibility and small-scale studies, often without dedicated analysis of pharmacodynamic interactions. Therefore, until high-quality evidence becomes available, we recommend that tES be used in combination with neuropsychiatric and non-neuropsychiatric pharmacotherapy only under conditions of careful clinical supervision.

Patients should be screened for medications known to directly or indirectly act on CNS and skin, and any changes in pharmacotherapy during tES treatment should be avoided whenever possible. Moreover, clinicians should evaluate whether a combined approach is likely to confer added clinical value on a case-by-case basis. Further studies are warranted to explore synergistic effects, pharmacological enhancement of tES efficacy, and safety across diverse drug classes.

9.6. TES combined with other non-pharmacological interventions

The administration of a concurrent non-pharmaceutical intervention can alter the brain state in turn modulating the effect and response of NIBS (Bradley et al., 2022; Opitz et al., 2015). The term “Non-pharmacological intervention” includes a variety of treatments. For the sake of this review, we followed the taxonomy proposed by Ninot et al. (Castellano-Tejedor, 2022; Ninot et al., 2017), who identifies five main groups, which are addressed below (for overview see Table S5).

9.6.1 Psychological Health Interventions range from prevention programs to psychotherapy interventions. Studies combined tDCS with fear conditioning paradigms, which are commonly used to model anxiety-related and broader emotional processes. Four studies used standard tDCS with different montages, all targeting the PFC (Dittert et al., 2018; Ganho-Ávila et al., 2019, 2022; Ma et al., 2024), and the inferior frontal gyrus (Ma et al., 2024) while one applied frontopolar HD-tDCS (Adams et al., 2023) to the DLPFC. All were single-session trials with young adults, conducted online or offline, using currents up to 1.5 mA. The combination was safe, with tDCS producing only mild AEs, such as itching, tingling, headache, skin redness, and tiredness. Blinding, when reported, was effective.

In a meta-analysis of 17 studies, 13 of which employed tDCS, NIBS combined with psychosocial interventions was found to be a safe approach for alleviating depressive symptoms (He et al., 2022). Commonly reported SEs included headache, scalp discomfort, skin redness, and itching, occurring in both active and sham stimulation groups. Most studies concluded that NIBS paired with psychosocial intervention is well-tolerated, with only mild and transient AEs, such as post-stimulation headache.

The safety and tolerability of NIBS, including tES combined with mindfulness-based interventions were evaluated in a recent meta-analysis by Demina et al. (Demina et al., 2024). The analysis reported good overall tolerability, no serious AEs, and generally high levels of treatment satisfaction.

One study combined tACS (delta-beta waveform) with behavioral activation, a third-wave evidence-based cognitive behavioral therapy in patients with depression. No safety concerns were noted (Carlton et al., 2025).

9.6.2. Physical Health Interventions. Five studies combined tDCS with physical training interventions in healthy young adults. (Thomas et al., 2021) applied tDCS during a combined aerobic and cognitive task but did not report collecting or analyzing AE data. In contrast, Jung et al. (2024), Lo et al. (2023), and (da Silva et al., 2019) implemented multi-session offline tDCS protocols (1.5 or 2 mA) during balance training, physical therapy, and time to exhaustion, respectively. All studies reported only mild AE and successful blinding. One study combined tRNS to the DLPFC and V1 with exergame training, with participants reporting no AEs (Moret et al., 2021). When reported, blinding was effective. Dumel et al. (2018) did not report collecting or analyzing AEs data, while the other studies reported only mild AEs.

In clinical populations, motor training combined with RS-tDCS has also shown efficacy. In individuals with impaired ambulation due to multiple sclerosis, 10 sessions of M1-targeted tDCS (2.5 mA) paired with aerobic exercise significantly improved gait speed and walking endurance, with benefits maintained four weeks post-intervention (Pilloni, Choi, Shaw, et al., 2020). A more recent trial demonstrated that 20 sessions of home-based, remotely supervised M1-SO tDCS paired with manual dexterity training improved hand function and MS-related quality of life in participants with impairment due to progressive MS, many of whom were also of older age (Pilloni et al., 2024).

9.6.3. Nutritional Health Interventions span from the use of dietary supplements to structured nutritional therapy and diet-based interventions. tDCS has been explored in combination with hypocaloric diets in individuals with excess weight. Natividade et al. (Natividade et al., 2021) reported only mild AEs, such as itching, tingling, and fatigue, with no significant differences in the frequency of AEs between active and sham groups. Similarly, Heinitz et al. (Heinitz et al., 2017) found a higher incidence of skin redness in the active tDCS group, while other mild AEs occurred at comparable rates across active and sham conditions.

9.6.4. Digital Health Interventions, encompassing wearable and handheld eHealth devices, therapeutic games, and virtual reality therapy, have been integrated with NIBS in training paradigms in recent studies. Specifically, four studies combined tDCS with various cognitive tasks (Duffy et al., 2024; Holczer

et al., 2023; Yu et al., 2020; Zhu et al., 2025), three studies combined tACS with working memory tasks (Diedrich, Kolhoff, Bergmann, et al., 2024; Diedrich, Kolhoff, Chakalov, et al., 2024; Krebs et al., 2021b), and two used tRNS (Brambilla et al., 2021; Chenot et al., 2022). All were conducted during stimulation, mostly using multi-session designs in young and older adults, with variable electrodes' montages, targeting the DLPFC. tDCS studies reported mixed cognitive findings and only mild sensations, similarly in active and sham groups (Ruf et al., 2017). Interestingly, while AEs remain mild, higher intensities generally cause more noticeable sensations (Weller et al., 2020). Two analyses from the "Augmenting Cognitive Training in Older Adults" study (Woods et al., 2018) found that 20 sessions of 2 mA tDCS over bilateral DLPFC were well tolerated, with only mild sensations (e.g., tingling, burning) and no other adverse events (Hausman et al., 2023a, 2024). While more participants in the active group reported high blood pressure, this was not attributed to stimulation (Hausman et al., 2023a), see also Section 7.4.

In the tACS studies, two participants experienced phosphenes (Diedrich, Kolhoff, Bergmann, et al., 2024; Diedrich, Kolhoff, Chakalov, et al., 2024). Two tRNS studies reported only mild sensations, but one participant dropped out because of a headache in the tACS group (Brambilla et al., 2021). Notably, Sheffield et al (Sheffield et al., 2022) conducted a multi-site review on blinding efficacy and AEs in studies combining cognitive training with NIBS. They found that AEs were more strongly associated with contextual factors such as testing site and session number, rather than the type of transcranial electrical stimulation itself. Blinding was less effective for tDCS and tACS compared to tRNS, particularly in conditions producing stronger cutaneous sensations. While smaller electrodes and repeated sessions did not increase AEs, the findings underscore the need for improved blinding protocols, especially in studies using higher-intensity stimulation.

In clinical populations, RS-tDCS paired with cognitive training has shown feasibility and cognitive benefits. In MS, studies report improvements in complex attention, reduced response variability, and enhanced cognitive outcomes after 30 sessions, particularly in those with greater disability (L. Charvet et al., 2018, 2025b; L. Charvet, Harrison, et al., 2023). In Parkinson's disease, two open-label studies demonstrated that RS-tDCS was safe, well-tolerated, and feasible for home-based delivery resulting in modest gains in processing speed, fatigue, and motor functions (Agarwal et al., 2018; Dobbs et al., 2018). Across both trials, tolerability was high, and adverse events were minimal and mild.

Two studies combined tDCS with activity performed in a virtual reality environment (Bulteau et al., 2017; Ciechanski et al., 2017), simulating height exposure or surgical resection, respectively, over one or two sessions, with a current intensity of 1 mA, reporting itching and tingling as the most common complaints, with no serious AEs (Ciechanski et al., 2017). Neri et al. (Neri et al., 2025) combined tRNS to the sensorimotor and visual networks with five days of a VR first-person shooter training, reporting only mild AEs and no differences between the active and sham groups.

We found no other health interventions (eg., phytotherapy, aromatherapy, etc) combined with noninvasive brain stimulation.

Conclusions and recommendations: The combination of tES with non-pharmacological interventions appears to be safe in adults across age groups. Reported AEs were mild and consistent with standalone tES applications. No significant safety concerns emerged across the reviewed studies. Despite these reassuring findings, differences in stimulation parameters and outcome measures limit the ability to draw definitive conclusions about safety in all contexts. Care must be taken when higher intensities are used to achieve successful blinding. In particular, a few studies did not systematically report or analyze AEs, showing the need for more rigorous and standardized safety monitoring. Given the wide range of potential interventions that can be combined with NIBS, it is essential that researchers implement rigorous monitoring and transparent reporting of AEs, particularly when evaluating novel combinations.

10. Ethical, legal and regulatory aspects

10.1. Ethics (doping, neuroenhancements, Neurorights)

In navigating the ethical landscape of tES, four core principles emerge: 1) rigorous safety, 2) equitable access, 3) strict oversight against misuse, and 4) protection of neurorights, all underpinned by comprehensive informed consent.

Firstly, adherence to established parameters, proper electrode preparation, and continuous monitoring is essential to minimise mild AEs (e.g., skin tingling, headache) and eliminate harms such as burns

(Bolognini et al., 2017). Secondly, tES therapies must be made available through regulated clinical channels, ensuring that socio-economic barriers do not exclude patients with a genuine therapeutic need (Voarino et al., 2016). The compliance of the health care personnel and the medical organisations to these technologies is essential in the successful implementation of the treatments (e.g. clinics buy tES devices but then lack the resources to keep them functioning). In terms of research and clinical use, the sensitivity to differences in populations in producing research data and implementing protocols to patients and participants need to be present. Equitable access, prevention of misuse, and protection of neurorights all concern wider frameworks than merely focus on the mental and physiological health of the patient. The implementation of treatment needs to acknowledge that values inherent in the technologies or values in the research data do not necessarily transfer from one society to another, from a given health care system to another and patients should not be ignored. One of the challenges for evidence based tES treatments is the ever changing (developing) devices: many treatment devices do not stay long enough to gather a good amount of evidence. Nevertheless, our aim is to comment on the tES protocols rather than on device-specific considerations.

Third, home-use systems require built-in lockouts, remote monitoring, and mandatory user training to prevent unsupervised off-label use and cognitive or sport "doping" in healthy individuals - a practice prohibited outside of approved research to ensure fair competition in academic, athletic, and professional settings (Voarino et al., 2016), although it is still unclear whether the benefit is a proven fact or a myth (Lefaucheur, 2019). Neuroenhancement using tES in healthy people is a frequently discussed issue, without official consensus (Antal et al., 2022). Finally, special consideration for vulnerable populations - particularly minors (See Section 7.3.) - requires age-appropriate consent processes and developmental risk-benefit analyses that respect emerging neurorights, including the right to mental privacy and cognitive integrity (Auvichayapat & Auvichayapat, 2022; Buchanan et al., 2022). Together, these principles ensure that tES remains a safe, patient-centred modality for therapy and rehabilitation, while minimising the risks of abuse, injustice, and exploitation.

10.2. Regulation of tES across the world

10.2.1. Europe

In the EU, in May 2021 the Regulation (EU) 2017/745 (<https://eur-lex.europa.eu/eli/reg/2017/745/oj/eng>), hereafter referred to as Medical Device Regulation (MDR), has superseded the previous medical device directive (MDD), and now regulates all aspects concerning "the placing on the market, making available on the market or putting into service of medical devices for human use and accessories for such devices in the Union" as well as "clinical investigations concerning such medical devices and accessories conducted in the Union." (Art. 1(1)). Importantly, according to Art. 1(2) the MDR also applies to "groups of products without an intended medical purpose that are listed in Annex XVI", where it explicitly lists under point 6. "Equipment intended for brain stimulation that apply electrical currents or magnetic or electromagnetic fields that penetrate the cranium to modify neuronal activity in the brain.", and Art. 1(3) details that "Devices with both a medical and a non-medical intended purpose shall cumulatively fulfil the requirements applicable to devices with an intended medical purpose and those applicable to devices without an intended medical purpose."

MDR Art. 2(1) rather widely defines a 'medical device' as "any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes: (1) diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease; (2) diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability; (3) investigation, replacement or modification of the anatomy or of a physiological or pathological process or state; (4) providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations; and (5) which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means."

Medical purposes relevant for tES devices are in particular the diagnosis, prevention, and treatment or alleviation of a disease (i.e., therapeutic applications), but also the investigation or modification of a physiological or pathological process or state (i.e., research applications), whereas for TMS also diagnosis

and monitoring purposes are relevant (e.g., via TMS evoked MEPs, TEPs, etc). It should be noted that there is a fundamental difference between the intended medical purpose (e.g., non-invasive stimulation of the human brain) and a specific clinical indication (e.g., major depressive disorder or chronic pain).

According to Art. 51(1), “devices shall be divided into classes I, IIa, IIb and III, taking into account the intended purpose of the devices and their inherent risks” and “classification shall be carried out in accordance with Annex VIII”. Following Rule 9 of the Annex VIII, “all active therapeutic devices intended to administer or exchange energy are classified as class IIa unless their characteristics are such that they may administer energy to or exchange energy with the human body in a potentially hazardous way, taking account of the nature, the density and site of application of the energy, in which case they are classified as class IIb”. Accordingly, tES devices, which qualify as active devices and have a comparatively low risk profile as outlined in this paper, fall into class IIa if they have a therapeutic medical purpose.

Notably, Rule 10 refers to “Active devices intended for diagnosis and monitoring. [...]” (not applicable to tES) and Rule 13 states that “all other active devices are classified as class I”. Unlike in the original definition in Art. 2(1), a rule explicitly referring to the medical purpose of “investigation” (as in academic or clinical research) is missing in Annex VIII, so that tES devices without a therapeutic purpose were automatically classified as class I (instead of the appropriate class IIa). Following a letter by six EU member states, based on an inaccurate risk assessment without proper review of scientific evidence and following a flawed line of argument, in 2022 the Regulation (EU) 2022/2347 (https://eur-lex.europa.eu/eli/reg_impl/2022/2347/oj/eng) re-classified all non-invasive brain stimulation devices without a medical purpose as class III, i.e., the highest risk category normally reserved for e.g., implantable devices, as it was reasoned that “while such equipment is not surgically invasive, the electrical currents or magnetic or electromagnetic fields do penetrate the cranium to modify neuronal activity in the brain.” Energy delivery to the body is, however, part of the definition of active therapeutic devices, which explicitly belong to class II, and, given the actual risk profile of tES devices provided in this paper, they more specifically belong to class IIa (see also the explanations provided by the Medical Device Coordination Group (MDCG) in document MDCG 2021-24, “Guidance on classification of medical devices”, (Directorate-General for Health and Food Safety, 2021). Therefore, both the evidence provided for an elevated risk of tES and TMS devices was incorrect (Antal et al., 2025) and the classification rationale was flawed. Unfortunately, this incorrect reclassification caused enormous irritations in the field and misinterpretations by regulatory bodies and regional ethic committees due to the unclear and ambiguous status of tES and TMS devices used for investigational research as medical purpose (cf. Art. 2(1)), rather than therapeutic or diagnostic applications (which are explicitly mentioned also in Rule 9 and 10 of Annex XVI). This confusion led to unjustified interruptions of research activities in many academic and clinical institutions. Researchers, clinicians, academic societies, manufacturers, and patient organizations have repeatedly expressed their concerns (Antal et al., 2024). Following a formal complaint to the EU Ombudsman and their respective recommendation in 2024 (<https://www.ombudsman.europa.eu/en/decision/en/185531>), the European Commission has asked the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) to issue a new evidence-based scientific opinion on the risk that is posed by using brain stimulation devices for non-medical purposes, which is expected to be published in 2026. Based on this opinion, the European Commission will hopefully re-reclassify non-invasive brain stimulation devices without medical purpose to the same class as those with a medical purpose, namely class IIa.

Since the MDR came into force in May 2021, manufacturers are required to conduct the conformity assessment procedure to obtain a CE-certification as a medical device for their product according to the MDR. However, since the notified bodies allowed to monitor the certification procedure and issue the CE-certificates simply cannot process the enormous numbers of re-certifications required, transition periods have been introduced and extended, e.g., to Dec 31 2028 for class II medical devices that previously did not require involvement of a notified body under the MDD. The CE-certification process requires the manufacturer to explicitly state the intended medical purpose as well as one or more clinical indications and to provide clinical evidence for the safety and effectiveness of the device. At the time of submission of this consensus paper, the first tES devices have received CE-certification as a medical device under the MDR with major depressive disorder as indication, and more are likely soon to follow.

Finally, there is a lot of irritation in the field regarding when research studies using a medical device, specifically a tES device, have to be conducted as ‘clinical investigation’ under the MDR (requiring registration with the national authorities, full compliance with ISO 14155 GCP, as well as costly and time consuming documentation, monitoring, and auditing activities) and when they may be conducted as mere ‘clinical study’ outside the MDR (i.e., only requiring a positive vote by the responsible ethics committee) (Rethwilm et al., 2024). An important tipping point in the decision tree is whether the study investigates the safety and/or performance of a specific investigational device (--> clinical investigation) or merely uses an existing medical device (which could in principle be replaced by another device with comparable features) as an auxiliary tool to investigate a fundamental neuroscientific or clinical research question (--> clinical study). For the latter, the medical device does not even need to be used for the medical purpose or the clinical indication originally indicated by the manufacturer. Unfortunately, while the MDR applies in all EU countries, the specific legal implementations of the regulation at the national level differ across EU member states, and even within each state, the local editorial committees often have their own interpretation regarding this issue, currently creating very unequal challenges for tES research across labs and countries within the EU.

10.2.2. Asia

Based on our research, no country in Asia has officially approved tES devices as medical devices, except for Singapore and South Korea. In 2017, Singapore's Health Sciences Authority granted Soterix Medical approval to market tDCS devices. These devices are approved for treating major depression and fibromyalgia (Soterix Medical Inc, 2025). Similarly, South Korea's Ministry of Food and Drug Safety (MFDS) approved the home-based tDCS treatment device MINDD STIM+ (Ybran Inc, n.d.) in 2021 for therapeutic use (Bikson et al., 2023).

In Japan, medical devices are categorized into four classes based on risk levels by the Pharmaceuticals and Medical Devices Agency (PMDA): Class I (extremely low risk), Class II (low risk), Class III (medium risk), and Class IV (high risk) (Medical Devices Agency, n.d.). For example, TMS devices are classified as Class II. Although tES devices would likely fall into a similar category, no such devices have been approved for medical use in Japan to date. The use of tES devices for basic or scientific research must comply with the Ethical Guidelines for Medical and Biological Research Involving Human Subjects, while clinical trials are governed by separate regulations. The Japanese Society for Clinical Neurophysiology issued safety guidelines for the research use of tES in 2019, which remain a critical resource for investigators using tES devices for research purposes (https://www.jstage.jst.go.jp/article/jscn/49/2/49_109/_article/-char/ja). However, the distinction between basic research and clinical trials can be ambiguous, raising the question of “where to draw the line between medical and non-medical use” (Antal et al., 2025).

Other Asian countries employ comparable risk-based classification systems. For instance, South Korea: The Ministry of Food and Drug Safety classifies medical devices into Classes I–IV based on risk (Food and Drug Administration, 2018); India: The Central Drugs Standard Control Organization uses a classification system ranging from Class A (lowest risk) to Class D (highest risk), as outlined in the Medical Devices Rules of 2017 (Central Drugs Standard Control Organization, n.d.); China: The National Medical Products Administration categorizes medical devices into three classes (I–III) based on increasing risk, as defined in the Rules for Classification of Medical Devices (The National Medical Products Administration, n.d.).

10.2.3. Australia

In Australia, medical devices are regulated through the Therapeutics Goods Administration and the Australian Register of Therapeutic Goods. Several devices are listed on the ARTG allowing for use, typically under clinical supervision. The Sooma tDCS/Transcranial electrical stimulation system was first listed in 2016 under an intended purpose of the treatment of “unipolar depression in the adult population under the supervision of a qualified health practitioner”. The neuroCare Group tES system was listed in 2017 but without a specific detailed therapeutic claim (“tDCS may represent an effective treatment option for patients presenting with major depressive episodes”). Finally, the Soterix Medical tES system has also been listed since 2017 with a lengthy description of application including “The device is intended to treat different neurological and psychiatric disorders. In particular, tDCS increases

spontaneous brain activity and metabolism in areas found to be hypoactive in patients suffering from major depressive disorder.”

10.2.4. America (USA & Canada)

In the USA, the framework comprises a system of regulations and recommendations issued by the Good Practices in Clinical Research, Code of Federal Regulations, and/or the Food and Drug Administration (FDA). The FDA defines medical devices as products that are “intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man... or intended to affect the structure or any function of the body...” The FDA’s classification for medical devices are based on risk level (Bikson et al., 2023; Food and Drug Administration, 2018). Class I devices are low-risk devices, such as band-aids, which are subject to general controls, such as registration of facilities and compliance with good manufacturing practices. Class II devices are moderate risk devices that are subject to additional special controls, such as performance standards and special labeling. Class III devices are those that pose a high risk of illness or injury. Most devices that provide a low level of electrical stimulation to the body for medical purposes, such as transcutaneous electrical nerve stimulation devices and powered muscle stimulation devices, are considered Class II devices (Fregni et al., 2015). However, tES devices without an intended medical purpose may not fall under the scope of FDA regulation (Antal et al., 2022; Vasquez & Fregni, 2021; Wexler, 2015).

Medical devices not cleared or approved by the FDA in the US are required to follow the Investigational Device Exemptions regulation (21 CFR Part 812). This regulation describes three types of device studies: significant risk (SR), non-significant risk (NSR), and exempt studies. Under 21 CFR 812.3(m), a SR device study is defined as a clinical investigation using a device that is intended as an implant, is represented to be for a use in supporting human life, is for a use of substantial importance in mitigating and treating disease or presents a potential for serious risk to the health, safety or welfare of a subject. A NSR device study is one that does not meet the definition for an SR device study. Certain studies are exempt from the requirements of 21 CFR Part 812, for example: studies of an already cleared medical device in which the device is used or investigated in accordance with the indications in the cleared labeling. Clinical trials using tDCS and tACS devices in the US have been generally classified as NSR. Sponsors of investigational SR device studies are required to get an approved IDE from the FDA before starting their study. In addition, in accordance with the regulations at Part 812, the study may not start until both FDA and the Institutional Review Board of clinical setting have given their approval.

Clinical Example – NYU Langone Health tDCS Telehealth Program: To meet growing clinical demand and align with regulatory standards, NYU Langone Health launched a telehealth-based RS-tDCS clinical service in 2019. This program operates under NSR designation and IRB oversight, offering home-based tDCS as innovative care for conditions such as multiple sclerosis, Parkinson’s disease, mood disorders, and post-stroke recovery. The protocol includes medical clearance, HIPAA-compliant remote supervision via video, and individualized treatment plans specifying electrode placement, current intensity, and dosing schedules. As of 2025, over 230 patients across 26 U.S. states have participated, completing more than 16,000 sessions. The program has demonstrated high engagement, safety, and feasibility, and serves as a model for large-scale implementation of RS-tDCS within U.S. healthcare systems.

10.2.5. America (South America)

In Brazil, tDCS devices are regulated as medical equipment requiring formal registration by the National Health Surveillance Agency (Fregni et al., 2015). Only NeuroConn’s DC-Stimulator is specifically ANVISA-approved for tDCS use (ANVISA certification is analogous to a CE mark). Clinical research must be approved by local ethics committees with possible review by the national regulatory body (Fregni et al., 2015).

Argentina’s National Administration of Drugs, Foods and Medical Devices (ANMAT) oversees medical device regulation and aligns with international health standards. tDCS devices would require ANMAT clearance; none are currently registered (<https://www.argentina.gob.ar/anmat/anmat-en/>). All clinical studies need institutional ethics committee approval.

Chile's Public Health Institute (ISP) manages medical device approval under national health law. tDCS equipment must comply with ISP standards and be registered. Research or clinical use of tDCS requires review by local ethics committees under Ministry of Health regulations.

Other South American nations follow similar models. For example, Colombia's INVIMA and Peru's DIGEMID regard tDCS equipment as medical devices, and Uruguay's health authority takes a similar stance; in all cases trials require ethics/IRB clearance.

10.3. Where should/could tES be performed and by whom?

TES can be applied in both clinical and non-clinical settings, serving different purposes such as treating patients, conducting clinical research, or advancing basic neuroscience by studying neurotypical participants in experimental brain research. In clinical contexts, tES may be administered in hospitals or private practices for evidence-based treatment of neurological and psychiatric conditions or as part of clinical trials involving patient populations. In non-clinical settings, tES is commonly used in research laboratories to explore brain function in neurotypical participants. Additionally, tES can be delivered outside a lab/clinic i.e. in home-based environments, either as part of remotely supervised research protocols or as prescribed clinical interventions. Given the diverse applications of tES, it is important to distinguish its use along three key dimensions: 1) participants: tES either being used in neurotypical adults, clinical populations or populations requiring special considerations (e.g. children); 2) settings: tES either being applied in research laboratories, clinical environments (e.g., hospitals or private practices), or home-based contexts; 3) personnel involved: tES either being administered by trained researchers, by healthcare professionals, or self-administered by participants, patients or non-professionals under or without remote supervision (for detailed consideration regarding home-based use see Section 10.4. and 10.5)

A primary consideration in determining where and by whom tES should be applied is the assessment of risk. Risk evaluation must account not only for the characteristics of the technique itself but also for individual participant factors such as potential vulnerability or the possibility of interactions with concurrent oral medications. In research contexts (e.g., academic institutions), tES is typically administered by trained personnel from diverse disciplinary backgrounds, most commonly biology, psychology, medicine and engineering. These individuals are required to have appropriate training, in order to independently perform tES (see Section 11). Ethical approval for such research applications must be obtained from the relevant institutional review board (IRB) or local ethics committee. In contrast, clinical applications of tES are subject to national regulatory frameworks, and formal approval from competent regulatory authorities may be required, where applicable (see Section 10.2).

Conclusions and Recommendations: When conducted in accordance with the safety standards and parameters outlined in previous sections, tES can be safely administered in clinical settings under the supervision of a healthcare professional or clinician, as well as in research environments by trained researchers under the oversight of a principal investigator with a medical or non-medical degree. Remotely supervised home-based tES (RS-tES) is also considered safe and offers the added benefits of increased accessibility and the potential to scale both research and clinical applications.

10.4. Remotely delivered tES - Home-based use under medical prescription or in research settings (Remote-Supervised tES)

The use of tES—particularly tDCS—in home settings has expanded rapidly, driven by the need to accelerate clinical trials, deliver scalable and accessible treatment options, and reduce the burden on healthcare systems. This approach is rapidly advancing research on optimal clinical use, safety, tolerability—especially over longer timeframes—and standardized implementation guidelines.

This successful implementation of guided home-based use has been facilitated by adherence to equipment and protocols that ensure reliable stimulation. The Remotely Supervised tDCS (RS-tDCS) guidance (L. E. Charvet et al., 2015, 2020) outlines 8 conditions, including staff training, to satisfy for home-based tES, which have been adopted in over 60 human trials (L. Charvet et al., 2018, 2025a; L. Charvet, George, et al., 2023; L. Charvet, Harrison, et al., 2023; Dobbs et al., 2018; George et al., 2025; Knopman et al., 2024; Pilloni et al., 2022, 2024, 2025; Richardson et al., 2023). Adopting these guidelines, a single center provided almost 7000 sessions in adults without significant AEs (Pilloni et al., 2022) and

a similar outcome was achieved by a study in pediatric populations (Simpson et al., 2022) with associated controls.

The eight RS-tDCS guidelines define minimum training requirements for researchers, clinicians, and staff, as well as criteria for equipment use and patient monitoring, to ensure the safe and consistent implementation of RS-tDCS protocols.

This section's conclusions are specified only for RS-tES (home based under medical prescription/research setting and following indicated guidelines). Digitalized tES is the integration of home-based tES with mobile-Health technologies (A. R. Brunoni et al., 2022), and when following RS-tES is within this section scope. So called "DIY-tDCS" (Wexler & Reiner, 2018) cannot be considered RS-tES due to the lack of ongoing supervision by a trained and experienced tES practitioner and provider. RS-tES interventions enhanced by feedback loops for personalization (e.g., adjusting stimulation parameters and session frequency based on symptom change or tolerability), or those integrating AI-based or other rule-based decision-support tools (e.g., IoT-enabled systems), should still be embedded within a broader connected care framework that includes active human supervision (Cohen Kadosh et al., In press). Securing human-factors by maintaining a clinician or researcher in the loop is essential to ensure safety, contextual interpretation of data, and clinical accountability.

RS-tES rules balance rigor with the need for flexibility. For example, the requirement for televisits during tES will vary between RS-tES addressing different indications and patient groups, ranging from at every session to only during orientation and certification. In contrast to self-directed home use, RS-tES requires ongoing professional supervision. For this reason, devices for RS-tES cannot continue to operate if professional supervision is discontinued (e.g., they are remotely deactivated).

Several additional studies support the safety and feasibility of RS-tDCS. Ruffini et al. (2024) showed that 34 of 35 patients successfully completed an 8-week program of left DLPFC stimulation for depression, including 4 weeks of daily treatment, with a 73% response rate and no AEs. Park et al. (2024) studied 19 patients for improvement in MCI after two weeks of tDCS therapy to the dorsal frontal cortex, with 3 patients experiencing minor burns that resolved over time. Ghazi-Noori et al. (2024) studied 44 persons with bipolar depression over 6 weeks with moderate success and mild AEs—mainly skin reactions such as redness (40.6%) or burning (26.5%).

One publication summarized six clinical trials at home. Pilloni et al. (Pilloni et al., 2022) amalgamated 308 subjects covering various disorders and 6779 RS-tDCS sessions. Participants tolerated treatment well, with only minimal mild AEs such as tingling (68%), itching (41%), and warmth (42%), equally reported in active and sham conditions. Class I RCTs demonstrated rapid enrollment, high adherence, and preserved blinding. Another review by Palm et al. (2017) amalgamated 22 clinical studies, again confirming minimal AEs.

Global feasibility of RS-tDCS is also being demonstrated. Silva-Filho et al. (Silva-Filho et al., 2022) discussed successful availability of RS-tDCS in middle-income countries, such as Brazil. Vogelmann et al. (Vogelmann et al., 2024) outlined a roadmap to developing at-home tDCS into a scalable tool for depression treatment.

As above, while tDCS remains under investigation status in the United States, a clinical care model for home-based tDCS has been successfully implemented at NYU Langone Health and other institutions offer both onsite and remotely accessible services under models of innovative care and outside of insurance coverage. Similarly, two studies were successfully conducted within the UK NHS using a RS-tDCS system complemented by digital psychological intervention, to treat major depressive disorder (and RCT with 174 participants (Woodham et al., 2024)) and perinatal depression (an open-label study with 25 participants (Griffiths et al., 2025)). Mild transient AEs occurred mostly in the active arm of the RCT and no serious adverse events were reported. This allows for the future of a prescription-based model for tDCS and tES treatment at home, typically paired with digital therapeutics and/or other rehabilitative exercises.

Recommendation: We recommend the adoption of the RS-tES guidelines, including provisions for staff and patient training and specialized equipment, in all clinical and research applications of RS-tES conducted under medical prescription or within research settings. This recommendation is supported by evidence from over 60 trials and thousands of RS-tDCS sessions across adult and pediatric populations

with varying levels of disability, demonstrating that adherence to the eight RS-tES guidelines (detailed below) ensures safety and feasibility without compromising scalability or accessibility.

RS-TES Guidelines:

- (1) General and study/treatment-specific tES training and certification of staff.
- (2) Criteria and procedures for screening and selection of patients/participants and/or caregivers, concerning their capability to participate in RS-tES-based interventions (include cognitive, psychological, physical and contextual prerequisites).
- (3) Training procedures and materials for participants and/or caregivers, including instructional materials, intervention administration and assessment of training effectiveness. Minimum competencies should be assessed by the research team/healthcare professionals, confirming suitability of the user. Consent forms for RS-tES, should include i) information importance of using equipment as directed, ii) data privacy, iii) information about remote monitoring and opt-out procedures.
- (4) Techniques for electrode preparation and placement to minimize risk of user error, including consistent montage for reproducibility
- (5) Equipment and procedures for reliable control of the prescribed stimulation dosage per session and across the entire intervention protocol. This includes all aspects of tES dose (Peterchev et al., 2012) (e.g. current intensity, waveform/time)
- (6) Routine monitoring strategies should be in place (with a schedule appropriate to the study objects and populations) to ensure adherence to the protocol, including consistent device setup, electrode saturation and placement, stimulation parameters and predefined corrective steps in case of deviations. When software is used to automate and manage dosing, procedures for staff oversight (review and changes) must be in place.
- (7) Methods for detecting, recording, managing and reporting any intervention-emergent AEs during or after tES sessions. RS-tES interventions should include procedures for access to a trained clinician or researcher, either in-person or via teleconference. Protocols should include standardized troubleshooting instructions and emergency response measures to manage potential AEs or protocol deviations.
- (8) Criteria for when individual sessions are discontinued such as due to discomfort, technical issues, or personal request, while remaining in the intervention, and criteria for when the intervention is discontinued (for instance, missing more than 20% of sessions (e.g., >4 of 20) or ≥ 3 consecutive sessions). All communications between patients, staff, and devices should protect guidelines for confidentiality and cybersecurity.

10.5. Safety and ethical aspects of freely available (direct-to-consumer) brain stimulation

Direct-to-consumer devices for brain stimulation are widely available for purchase online (Wexler, 2015, 2020), at least in some societies. To date, there have been three studies of users of direct-to-consumer tES devices (Jwa, 2015; Wexler, 2016; Wexler & Reiner, 2018). All found that users generally adhered to the current levels (1–2 mA) and typical length of stimulation session (20 min) used in scientific studies at the time. Home users did, however, depart from conventional protocols with regard to number of sessions: Wexler (2018) found that 40% of respondents had self-administered over 21 sessions of tDCS. Among them, 8% were “super-users” who reported over 100 sessions of tDCS. Approximately one-third of respondents reported skin irritation and 3% of users reported significant skin burns (Wexler & Reiner, 2018). Thus, while to some extent, home users adhere to the current levels employed in scientific studies, they tend to experiment with the conventional duration and number of sessions. This of course raises questions of safety, effectiveness and unintended effects on the users. Even if the use is typically well tolerated during a session, this does not preclude the possibility of long term AEs arising due to frequent and/or repeated stimulation, particularly in the case of “super-users” who experience a large cumulative ‘dose’ (see also (Riggall et al., 2015)).

Aside from self-reported studies of users, there is little peer-reviewed scholarship examining the safety or effectiveness of direct-to-consumer tES devices. One study found that stimulation with the Foc.us v1 device caused subjects to perform worse on the accuracy component of a working memory task than subjects who received sham (Steenbergen et al., 2016); other studies have assessed the efficacy of Halo

Sport for enhancing aspects of athletic performance (Jiang et al., 2022; Lu et al., 2021) or the Thync device (Paneri et al., 2016). However, none of these devices are currently available on the market.

One company, Flow Neuroscience, exemplifies how the lines between medical use and the freely available direct-to-consumer devices are increasingly blurred. The company markets a CE-certified tDCS device, which has shown mixed results for depression in clinical studies (Borrione et al., 2024; Woodham et al., 2024). Flow is sold directly to consumers in the EU, UK, Norway, and Hong Kong, accompanied by a smartphone app offering behavioral therapy. The device includes built-in usage restrictions: during the first three weeks, users can administer up to five sessions per week, followed by a limit of two sessions per week thereafter.

On a general level, the debate about treatment versus enhancement is still ongoing and use of these direct-to-consumer devices for enhancement have their own ethical aspects (Voarino et al., 2016). This debate also bears relevance to health care systems and there are arguments for promoting access to technologies that increase well-being regardless of whether they are for treatment or enhancement purposes (Zohny, 2014). Engineering (manufacturers) standards have been proposed that apply to all limited-output tES devices including direct-to-consumer products (LOTES), which suggest medical-grade risk management and precise labeling (Bikson et al., 2018, 2023).

Conclusions and recommendation: More data is needed regarding the safety and efficacy of direct-to-consumer brain stimulation devices marketed to the general public. We recommend distinguishing between direct-to-consumer devices manufactured respecting medical-device standards and those with no evidence for quality control.

10.6. Blinding efficacy - Placebo stimulation

Establishing adequate sham conditions and maintaining blinding integrity are critical for ensuring the validity of safety data in randomized controlled trials using tES. Inadequate blinding may not only compromise the interpretability of efficacy results, but also obscure whether reported SEs or AEs are attributable to the stimulation itself or to psychological or other nonspecific factors. Despite this importance, the evaluation of blinding success has historically been neglected in clinical research in general; only 2% of randomized trials across medical disciplines tested blinding success as of 2001.

In tES studies, participants may perceive physical sensations such as scalp tingling or itching, potentially enabling them to correctly guess whether they are receiving active stimulation. Neuromodulation studies, including those using tES, are susceptible to this issue (Knotkova et al., 2021). A review of screened papers consisting of 35 randomized controlled trials published after the previous tES safety guideline examined whether blinding integrity was assessed. Of these, 16 studies (45.7%) included assessments of blinding success, typically by asking participants whether they believed they received real or sham stimulation (Cherney et al., 2021; daSilva Morgan et al., 2022; Flynn et al., 2024; Gehrman et al., 2024; Lee et al., 2022; Leffa et al., 2022; Manor et al., 2018; Nikolín et al., 2020; Pereira et al., 2021; Sampaio-Junior et al., 2018; Shaw et al., 2020; Smeele et al., 2023; Valiengo et al., 2017, 2020; Wandrey et al., 2023; H. Wang et al., 2019). The remaining 19 did not report such assessment.

While most of these studies reported blinding success, notable exceptions exist. For example, Leffa et al. (2022) observed that participants in the active tDCS group guessed their condition more accurately than expected by chance. Cherney et al. (2021) reported that all four participants in the sham group mistakenly believed they received active stimulation. Nikolín et al. (2020) found statistically significant differences in participant guesses between sham and active tRNS groups, indicating inadequate blinding despite limited impact on outcome measures.

The effectiveness of a sham will depend on several factors: 1) the goals of the trial and how sham is assessed (e.g. subject's guess on condition), 2) the equipment (electrodes) and other protocol details (e.g. participant instructions, distractors), and 3) the sham protocol itself. Given this variability, sham designs may reasonably vary across trial contexts. However, the literature indicates that, when participants are explicitly asked, physical sensations during tDCS and sham stimulation are often different, potentially leading to decrease blinding efficacy (Bjekić et al., 2024; Greinacher et al., 2019; Turi et al., 2019). This highlights the need for context-specific validation of sham protocols and transparent reporting of blinding integrity.

Conclusion: Sham protocols used in the field do not raise safety concerns per se. However, proper sham and blinding procedures are essential for evaluating the safety of tES. Building consensus toward the harmonization of sham methodology remains an important goal to support valid and ethical safety evaluations.

11. Training and certification programs: Assuring safety in the future

The favorable safety profile and ease of use of tES make it appealing for clinical applications and research. Still, proper training is necessary to ensure the correct use of the device, knowing how to prevent possible AEs and how to deal with them should they arise. While clinical treatments should obviously be supervised by respective health care professionals there is no requirement for a specific occupation for persons doing the stimulation or medical supervision in a research setting if proper training has been ensured.

The proper training ensures the acquisition of theoretical and practical knowledge about tES. For example, researchers should know the principles of tES and the physiology of its wanted and unwanted effects. Furthermore, researchers, technicians and even research participants/patients themselves, in the setting of home use, would need to know how to set up the equipment, how to place the electrodes correctly, and how to assure the prescribed dose of stimulation. After a period of instruction, individuals should be assessed to make sure they can do all the procedures correctly. It might help compliance in certain settings to have the instructor and the trainee sign the same document confirming the satisfactory completion of the training.

It is of note that improper protocols may be associated with subjective reports of atypical pain, so protocols may include a session termination rule based on a pain level. Though the *perception* of heat is not associated with a risky increase in skin temperature (Khadka et al., 2018), proper training is necessary to ensure adequate reaction. In certain circumstances, it would be appropriate to know how to deal with cognitive or emotional changes that also may occur, such as participants/patients feeling uneasy or anxious during the procedure. Persons performing tES should follow SOPs, that prescribes notification paths and procedures for reporting AEs.

12. Statement from tES manufacturers / Manufacturers perspective

“THE HEALTH AND WELL-BEING OF MY PATIENT will be my first consideration;” This is an excerpt of the physician’s pledge from the Declaration of Geneva (“Declaration of Geneva,” 2025), which describes the many ethical implications to which physicians are bound. These ethical standards apply to the development of devices for our field of low-intensity tES. Most of our companies work already according to ISO 13485 standard, which outlines a Quality Management System (QMS) for the medical device industry. This standard emphasizes patient safety by maintaining consistent quality throughout the entire lifecycle of medical devices and it is recognised globally by various organisations and regulatory bodies (International Organization for Standardization, 2016). We believe that a well-regulated market is essential for the sustainable growth of industry, and we welcome regulation based on principles like the EU’s Better regulation framework (Antal et al., 2024). However, any legislation must be based on real, solid scientific evidence or comprehensive data from all market participants and not on arbitrary, quickly compiled and superficial data. Everyone must be able to rely on official authorisations as a reliable indicator of the safety, efficacy and reliability of products.

Safety of patients and users is of paramount importance (for us) when developing devices for medical, non-medical and research use. This involves rigorous testing, clinical and safety trials and continuous post-marketing surveillance of devices.

Developers from our industry must ensure that devices do not pose unnecessary risks and that potential risks are clearly communicated to providers, users and patients. Therefore, we as the manufacturers of those devices must identify the hazards associated with the medical device and devices without an intended medical purpose, to estimate and evaluate the associated risks, to control these risks to the maximum technical possible, and to monitor the effectiveness of the controls. The requirements of the risk analysis are applicable to all phases of the *life cycle* of a *medical device*. The *process* described in the standard applies to *risks* associated with a *medical device*, such as *risks* related to biocompatibility, data and systems security, electricity, moving parts, radiation, and usability. A risk management process is

therefore mandatory for every tES device brought to the market, ensuring safety and performance (International Organization for Standardization, 2019). Further, manufacturers of low-intensity tES devices already provide their users with instructions for safe handling of the technology, the proper labeling as well as the duration and strength of the applications as well as information on SEs and contraindications.

Our field of low-intensity tES and software for Digital Health will come closer together. The medical device industry will be undergoing a transformation in the future. With artificial intelligence, wearables, digital diagnostics, connected health platforms, and robotics, devices in our field are becoming smarter, more precise, and deeply integrated into patient care. This brings new ethical and legal challenges to the development of low-intensity tES in the future. However, these technologies will offer significant benefits, such as personalized treatments, but they also raise concerns about algorithmic bias, transparency, and accountability.

Post market surveillance is a tool to monitor safety, performance and effectiveness of any device placed on the market and to install a proactive and systematic process as required in ISO 13485 / MDR / FDA in order to derive the necessary corrective and preventive action (CAPA). Companies in our sector often have large data sets on the real-world use of NIBS devices, which could provide insights into their safety and performance to regulators monitoring them, but also to researchers and the public (International Organization for Standardization, 2016).

Recommendations: Companies certified acc. to ISO 13485 demonstrate their ability to design, develop, produce, install and service safe devices for low-intensity tES. According to international understanding, the classification of medical devices is a risk-based system that takes into account the vulnerability of the human body and the potential risks associated with the devices (Antal et al., 2024). By following the regulation and state of the art, there is no a priori difference in risk between medical, NIBS devices without an intended use including research devices. Different classifications on safety within a regulatory framework are therefore unnecessary since the risk level is the same. Technical standards on low-intensity tES are necessary to address specific aspects of safety and performance for various types of such devices (Bikson et al., 2023). Post Market Surveillance data sets from manufacturers of medical devices and devices without an intended medical purpose for our field of low-intensity tES should be included in publications on safety since they include basic information on quality and safety and maybe also on performance. Open cooperation with all stakeholders must be sought in order to find an efficient set of rules for all parties involved in the ongoing digitalization of our field. The FDA's very pragmatic approach in the US, which already allows the local ethics committee to classify low-intensity tES studies as non-significant risk studies (Food and Drug Administration, 2018), will continue to make it easier for local scientists to expand the parameter range of low-intensity tES devices as in (Cassarà et al., 2025) or to study their interactions with other modalities when a NIBS device is classified as a non-significant risk device. In this way, preclinical, safety and efficacy data can continue to be obtained quickly and efficiently, which is essential for successful collaboration between industry and academia to enrich the overall research process.

13. Monitoring procedures for tES

13.1. Note on serious and unexpected side and adverse events

As with any research or clinical intervention, participants may experience AEs that occur during the course of the study or treatment but are unrelated to the intervention itself. This may include physical accidents, psychological distress, decreased well-being, disease onset, or any other unfortunate life events that coincide temporally with tES application. In this regard, Kumar et al. (Kumar et al., 2022), who combined 2 mA anodal tDCS daily over 5 days with swallowing exercises in post-stroke dysphagia reported that three patients did not complete the study on dysphagia due to unrelated deaths, which were appropriately documented as part of good clinical reporting. A self-described case report (Aguilar-Ramirez et al., 2009) describes the emergence of lucid dreams, déjà vu, anxiety, and panic attacks 3 weeks after a cognitive tES experiment. This person later developed neurological symptoms and was diagnosed with epilepsy, but no link between symptoms and tES has been established. Regardless of the severity, the procedures for monitoring and reporting of AEs must be rigorously implemented. On this note, Kumpf-Vogelmann et al (Vogelmann et al., 2025) reported the premature termination of a clinical

trial of home-use tES in depression treatment due to an accumulation of AEs. Several patients experienced skin lesions and safety monitoring was insufficient to detect or prevent AEs. Skin burns can occur if electrodes are improperly designed or employed and so are not an expected AE in conventionally designed tES interventions (Woods et al., 2016).

In conclusion, while serious or unexpected AEs can occur in any clinical or research context, particularly among older or medically complex populations, there is no evidence to suggest these are caused by tES itself. Still, even if unrelated, these rare incidents should be reported in line with good research and clinical practice, and following national and institutional regulatory standards.

13.2. Participant/Patient Screening

Prior to including a participant in a study/a patient for treatment using tES, investigators/clinicians should assess the exclusion criteria using a standard questionnaire. Consensus was reached for the following questionnaire (Table 2). The current screening questionnaire is an updated version of the one proposed in Antal et al. (2017) and is recommended for use, when applying tES in research and clinical settings. An affirmative answer to the first question (i.e., skin) constitutes an absolute contraindication to tES and the rest of the questions listed refer to relative exclusion criteria depending on the study population and the objectives or the clinical goals (see Section 8). In line with the Declaration of Geneva, it is the responsibility of the principal investigator or the attending physician to assess each participant/patient's health and well-being as their primary concern.

<<Table 2 about here>>

13.3. Side Effect and Adverse Event Reporting

One of the crucial measures in ensuring safety and tolerability of the stimulation protocols in a study using tES is the active query of SEs and AEs [refer to Section 2.1 for further details on understanding SEs and AEs]. Standardized questionnaires implementing numerical scales to assess and rate the severity of AEs have been previously recommended (Antal et al., 2017; A. R. Brunoni et al., 2011; Fertoni & Miniussi, 2017; Poreisz et al., 2007). However, the internationally adopted standardized approach for SE/AE recording and reporting is yet to be established.

It is important to address the fact that in the vast majority of studies, AEs are assessed after stimulation only, and no baseline assessment of potential AEs as already existing symptoms is done. This is why, when only "after-tES" assessments are done, many times it is difficult to decide whether an AE is related to tES or simply this symptom (e.g., tiredness) has already existed before the session. This could be one of the explanations for the discrepancies in the AE frequencies reported across studies.

Recommendation: Given the reported SE/AE, researchers and clinicians are strongly advised to monitor and evaluate the following symptoms before, during and after tES application: skin sensations (tingling, itching), headache/scalp pain, pressure under electrode, fatigue/sleepiness/trouble concentrating, warming sensation/heat, negative mood, neck pain/stiffness, nausea, lightheadedness, flickering lights, vibration perception under the electrodes. Furthermore, it is advisable to monitor and record not only potentially unpleasant but also possible positive SEs such as: alertness, calmness, positive mood, sense of wellbeing, increased concentration. The protocols should be established so that if negative SEs or AEs persist beyond the immediate post-stimulation period, participants can notify the investigator, who will then assess the severity and decide whether to continue the stimulation or take another appropriate action.

13.4. Acceptability of tES

Studying patient's acceptability of an intervention is important in health innovation, as higher acceptability by patients and health professionals increases the adherence to prescribed recommendations, including safety procedures by patients/careers and clinicians/prescribers/technical assistants, consequently improving overall results (Borrelli et al., 2005; Hommel et al., 2013; Peters et al., 2013; Proctor et al., 2009). Importantly, acceptability assessments in tES need to go beyond drop-out rates and limitations to accessibility. The Theoretical Framework of Acceptability (Sekhon et al.,

2017) offers a broader definition of acceptability that include seven components: the affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs and self-efficacy. Moreover, as tES in health innovation moves increasingly toward digital health, with growing reliance on remote clinical oversight with AI-based systems for diagnosis and personalization of treatment, new challenges emerge that should be integrated in acceptability measures. Key factors related with hybrid and digital interventions are outlined in the Digital Therapeutic Alliance framework (Malouin-Lachance et al., 2025) and include empathy and trust, personalization, therapeutic agreement, treatment goals, and ethical concerns.

Recommendation: Future clinical studies should include well-grounded and comprehensive assessments of acceptability. Theoretical models such as the Theoretical Framework of Acceptability and the Digital Therapeutic Alliance framework (for studies involving digital components) provide reliable foundations for developing such measures.

14. Summary and final conclusions

In conclusion, this review provides an updated and comprehensive synthesis of the safety evidence for low-intensity tES, based on studies published between 2017 and 2024. It integrates data from animal studies, computational modeling, and human trials in both healthy and clinical populations, including vulnerable groups (children, older adults, pregnant women) and special stimulation conditions (e.g., home-based use). Overall, common mild AEs associated with low-intensity tES include skin redness (erythema) and paraesthesias (e.g., tingling, itching, burning), whilst other symptoms reported in the literature (e.g. skin sensations, headache, fatigue, etc.) are typically same as those seen with sham protocols. Before stimulation starts, carefully screening the skin for diseases or focal lesions in the area of stimulation, is recommended.

Current evidence supports the continued classification of tES as a low-risk intervention when used within established safety parameters. As such tES can be used in research and clinical settings by trained non-medical and medical professionals. As the field expands and its applications diversify, a key challenge is to maintain an appropriate balance between regulatory oversight and scientific advancement. Regulatory frameworks must ensure human protection and minimize the risk of misuse, while simultaneously enabling and facilitating basic and translational research. Overly stringent or misapplied regulations, particularly in non-clinical research settings involving healthy volunteers, may impede methodological innovation and hinder the development of the field, including the advancement of therapeutic applications of tES. In contrast, inadequate oversight and regulation may lead to misuse and expose people, particularly those with mental health problems, to physical, psychological, and financial harm. Accordingly, this review highlights the need for clear, nuanced guidelines that distinguish between clinical and non-clinical use, and take into account contextual factors such as setting, population characteristics and stimulation protocols. In addition, the implementation of standardized SE and AE monitoring and reporting practices, harmonized regulatory procedures, and structured training requirements are essential to ensure the responsible, safe, and effective use of tES in both research and clinical settings.

15. Annexes

Literature search syntax

PubMed

syntax: ((((((safety[Title/Abstract]) OR (side effect*[Title/Abstract])) OR (adverse effect*[Title/Abstract])) OR (tolerability[Title/Abstract])) AND ((((((tES[Title/Abstract]) OR (transcranial electric* stimulation[Title/Abstract])) OR (tDCS[Title/Abstract])) OR (transcranial direct current stimulation[Title/Abstract])) OR (tACS[Title/Abstract])) OR (transcranial alternating current stimulation[Title/Abstract])) OR (transcranial random noise stimulation[Title/Abstract])) OR (tRNS[Title/Abstract]))) AND (2017/1/1:3000/12/12[pdat]))

The initial set of records: ([link to the OSF](#))

The final set of records with abstracts: ([link to the OSF](#))

Examples of topic specific searches:

Ageing:

The following search string was used: ((((((safety[Title/Abstract]) OR (side effect*[Title/Abstract])) OR (adverse effect*[Title/Abstract])) OR (tolerability[Title/Abstract])) AND (((((((tES[Title/Abstract]) OR (transcranial electric* stimulation[Title/Abstract])) OR (tDCS[Title/Abstract])) OR (transcranial direct current stimulation[Title/Abstract])) OR (tACS[Title/Abstract])) OR (transcranial alternating current stimulation[Title/Abstract])) OR (transcranial random noise stimulation[Title/Abstract])) OR (tRNS[Title/Abstract]))) AND (2017/1/1:3000/12/12[pdat]) AND ((Healthy aging) OR (healthy ageing) OR (older adults) OR (elderly))

Combination with nonpharmacological treatments:

((((safety[Title/Abstract]) OR (side effect*[Title/Abstract])) OR (adverse effect*[Title/Abstract])) OR (tolerability[Title/Abstract])) AND (((((((tES[Title/Abstract]) OR (transcranial electric* stimulation[Title/Abstract])) OR (tDCS[Title/Abstract])) OR (transcranial direct current stimulation[Title/Abstract])) OR (tACS[Title/Abstract])) OR (transcranial alternating current stimulation[Title/Abstract])) OR (transcranial random noise stimulation[Title/Abstract])) OR (tRNS[Title/Abstract]))) AND (2017/1/1:3000/12/12[pdat]) AND ((training) or (exercise) or (diet) OR (repetition) OR (practice) OR (neuroenhancement) OR (neuro-enhancement) OR (enhancement) OR (combination))

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Tables

Table 1. Summary of SE/AE across different tES techniques, with severity, frequency of occurrence and respective SE/AE classification i.e. grading in line with definitions outlined in [Section 2.1](#)

Effect	Affected Area	Severity	Frequency	Stimulation Types	SE/AE grade	Notes
Tingling/Itching	Scalp	Mild	Very Common	tDCS, tACS, otDCS, tsDCS	SE/AE Grade 1	Transient, higher with tDCS and with higher intensities; reduced with longer ramping; present in sham.
Burning sensation	Scalp	Mild to Moderate	Common	tDCS, otDCS, tsDCS	SE/AE Grade 1	Linked to electrode contact; more common with poor electrode preparation or repeated sessions.
Skin redness	Scalp	Mild	Common	tDCS, HD-tDCS, tsDCS, tACS	SE/AE Grade 1	Temporary; persistent with accelerated protocols; irritation or dermatitis.
Phosphenes	Perceptual Visual Field	Mild	Common with tACS	tACS, otDCS	SE/AE Grade 1	Frequency dependent; stronger when electrodes are closer to the eyes; usually not distressing.
Visual flickering/ Distortion	Perceptual Visual Field	Mild	Occasional	tACS	SE/AE Grade 1	Frequency dependent effect, during stimulation, not harmful.
Headache	General	Mild	Common	tDCS, tACS	AE Grade 1	Self-resolving, timely, linked to stimulation sessions.
Fatigue/Sleepiness	Systemic	Mild	Common	tDCS, otDCS, tACS	AE Grade 1	Reported more in older adults and in postpartum women.
Dizziness/Vertigo	Vestibular	Mild	Uncommon	tACS	AE Grade 1	Low frequency vestibular effects; short duration, reversible.
Local pain or discomfort	Scalp	Mild	Common	All	AE Grade 1	Usually due to electrode placement, wrong electrode preparation or stimulation start.
Difficulty concentrating	Cognitive	Mild	Rare	tDCS	AE Grade 1	Mostly self-reported, short-lived.
Contact dermatitis	Skin	Moderate	Occasional	Accelerated tDCS	AE Grade 2	Observed in prolonged/accelerated protocols.
Mood changes (e.g. Hypomania)	Mood	Moderate	Rare	tDCS in MDD	AE Grade 2	In patients with depression; causal link unclear.

Table 2: Screening questionnaire for transcranial electrical stimulation.

Screening Questions		Yes	No
Absolute exclusion criterion			
1	<p>Do you have open wound(s), preexisting skin disease (e.g., nevi, angiomas or previous burns/scars, neurodermitis, etc.), or active infection at [<i>specify the stimulation sites e.g. on the head</i>]?</p> <p>If yes, please specify the issue and location:</p> <p>_____</p> <p><i>Note: Assess if it can lead to increased risk of skin irritation, damage, or secondary infection associated with tES and/or the use of conductive gel/paste/solution; if yes – exclude.</i></p>		
Relative exclusion criteria			
1	<p>Do you have any metal or electronic implants (e.g. splinters, fragments, clips, cochlear implants, deep brain stimulation, metallic tattoo, etc.) in the brain/skull. If yes, please specify the type of metal and the location.</p> <p>_____</p> <p><i>Note: Tooth fillings and braces are no exclusion criteria</i></p>		
2	<p>Do you have metal or any electronic device at other sites in the head, neck, or chest area, such as a cardiac pacemaker or traumatic metallic residual fragments? If yes, please specify the location or device</p> <p>_____</p>		
3	<p>Have you ever had unexplained or repeated loss of consciousness? If yes, please describe:</p> <p>_____</p>		
4	<p>Have you ever had seizures and/or seizure activity in the past year? If yes, please describe:</p>		

5	Have you ever had a head trauma followed by impairment of consciousness?		
6	Do you have a history of migraines or frequent headaches?		
7	Do you have known neurological or psychiatric disorders (including alcohol, medication, and drug dependence or abuse). If yes, please specify: _____		
8	Are you currently pregnant or is there a chance that you might be?		
9	Are you breastfeeding?		
10	Do you have a history of surgical procedures involving your head or spinal cord? If yes, please specify the locations: _____		
11	Did you have major surgical procedures in the past 2 months. If yes, please specify: _____		
12	Do you take medication? If yes, please specify: _____		
13	Did you have low tolerability of previous tES applications? If you have never had tES before answer NA		

The questions 2 through 13 are proposed as a question pool that can be expanded or reduced depending on the specific context and purpose of the tES application. An affirmative answer to one or more of these questions does not constitute an absolute contraindication to tES. In line with the Declaration of Geneva, it is the responsibility of the Principal Investigator or the attending physician to assess each participant's health and well-being as their primary concern.

Supplementary materials**S1: Summary of studies performing network-targeted tES. The table shows the main characteristics of the protocol and the main reported side effects.**

Reference	Targeted network	tES modality	Number of electrodes (Max)	Total injected current (mA)	Max current per electrode (mA)	Electrode	Duration (min)	N	Population characteristics	Reported side effects
Mencarelli, 2020	Sensorimotor network (SMN)	tDCS	8	4	1.843	Saline sponge (3.14 cm ²)	22	20	Healthy	Sleepiness Tingling under electrodes Mild burning Headache Changes in mood Neck pain Scalp pain Trouble concentrating
Fischer et al, 2017	Resting state fMRI network associated with primary motor cortex (M1)	tDCS	8	4	1.851	Ag/AgCl with gel (3.14 cm ²)	10	15	Healthy	Mild tingling Warmth Itching
Zhou, R. et al, 2022 and Wei, X et al, 2024	Dorsal Attention Network (DAN), Default Mode Network (DMN)	tDCS	7	4	2	Ag/AgCl with gel (3.14 cm ²)	20	48, 40	Healthy	Pain Tingling Itching Skin reddening
Ester-Nacke, T. et al, 2024 and Ester-Nacke, T. et al, 2025	Hypothalamus appetite-control network	tDCS	12	4	2	Ag/AgCl with gel (3.14 cm ²)	25	10, 44	Healthy	Tingling Itching Pain Exhaustion
Adhia, D. et al, 2022	pgACC, dACC, somatosensory cortices (S1)	tACS + tRNS	8	4	1 (carrier)	Ag/AgCl with gel (3.14 cm ²)	30	30	Neurologically healthy (lower back pain)	(Most common in active) Headache

										Fatigue
Smeele, S. J. et al, 2022	Auditory cortex (AC), parahippocampus (PHC), and posterior cingulate cortex (PCC)	tACS + tRNS	9	4	1.5 (carrier)	Ag/AgCl with gel (3.14 cm ²)	30	20	Chronic tinnitus	Tingling Burning sensation Dizziness Headache Nausea
Goede, L. L. et al, 2024	Parkinson's Disease response network	tDCS	14	≤4 mA	≤2 mA	Ag/AgCl with gel (3.14 cm ²)	20	21	PD patients	Mild tingling
Abellaneda-Pérez, K. et al, 2021	Two cognitive networks	tDCS	8	4	1.705	Saline sponge (8 cm ²)	30	31	Healthy (elderly population)	Not mentioned explicitly, but no significant differences were found between the three stimulation conditions.
Chou, T. et al, 2020	Default mode network (inferior parietal nodes)	tDCS	8	2	1	Ag/AgCl with gel (3.14 cm ²)	30	90	Healthy	No AEs were reported.
Dagan, M. et al, 2018	IDLPFC + M1	tDCS	6	3	1.5	Ag/AgCl with gel (3.14 cm ²)	20	20	PD patients	No AEs were reported.

S2. Original studies investigating the effect of tES in neuropsychiatric symptoms or diagnosis during pregnancy

	Shenoy et al 2014	Trevizol et al., 2015	Sreeraj et al, 2016	Strube et al., 2016	Vigod et al., 2019	Wilkening et al, 2019	Kurzeck et al., 2021	Laurin et al., 2022. (cas e report 1)	Laurin et al., 2022. (case report 2)	Zhao et al., 2022
Study Type	Case Report	Case Report	Case Report	Case Report	RCT	Case report	Open label	Case report	Case report	RCT
Type of tES	tDCS	TNS	tDCS	tDCS	tDCS	tACS	tDCS	tDCS	tDCS	tDCS
Diagnosis/Symptoms	Auditory hallucinations in schizophrenia	PPD	PPD	Auditory hallucinations in schizophrenia	PPD	PPD	PPD	bipolar type 2 depressive disorder	PTSD	Peripartum mental health symptoms
N	1	1	1	1	10 (+10 sham)	1	6	1	1	62 (+64 sham)
Dropouts	—	—	—	—	2 (+2 sham)	—	—	—	—	0 (+0 sham)
Concomitant medication	Add-on (Iloperidone 12-mg per day)	No	No	No	No	No	No	Add-on (lamotrigine (100-mg/day)	Add-on (Venlafaxine (75-mg/day) + reading traumatic script	Drugs for lumbar anesthesia Bupivacaine only [n = 52] or Bupivacaine with Lidocaine [n = 10]
Trimester	2nd	2nd-3rd	1st	3rd	2nd-3rd	1st	1st-3rd	1st	1st	3rd

Parameters	Anode midway between F3-FP1; Cathode midway between T3 and P3; 2 mA, 20 min; two sessions/day	supraorbital trigeminal branches (V1) bilaterally; 120 Hz; daily	Anode over F3; Cathode over F4; 2 mA; 30 min; daily (with one day break after session 8) 10 days	Anode over F3; Cathode over Tp3; 2-mA; 30-min; twice daily, 3-hour interval; 2 weeks	Anode over F3; Cathode over F4; 2 mA; 30 min; 1/day, 5 days/week; 3 weeks	Anode over F3; Cathode over F4; 2mA, 48 000 cy cles, 40Hz; daily?	Anode over F3; Cathode over F4; 2 mA; 30 min; 20 twice daily + 10 daily	Anode over F3; Cathode over F4; 2 mA; 30 min; daily; 3 weeks	Anode over F3; Cathode over Fp2; 2 mA; 30 min; twice daily (30 min between sessions); 5 days	Frontal skull (unspecified); 2 mA, 20 min; 1 session
N. of sessions	10	10	10	20	15	9	30	15	10	1
Adverse events to the mother	No significant AEs	Not reported	Transient, mild burning sensations at application site and transitory experience of phosphenes	No reported or noticeable AEs or unexpected effects	Not reported	Mild phosphenes during stimulation	Mild headache during and after stimulations; itching sensation beneath the electrodes; insomnia (probably unrelated to tDCS); phosphenes (3 patients)	Fatigue and paresthesia	Tingling, difficulty concentrating, fatigue, scalp pain, itching, burning, and redness	No between group differences except for increased dizziness for active group
Adverse effects to the foetus	Not observed	Not reported	Not reported	No reported or noticeable AEs or unexpected effects	1 preterm birth	Not reported	Not observed	Not observed	Not observed	No between group differences

Follow-up safety data	Not observed	At three months: no complications	—	At 35th gestational week: no complications	At at 4 and 12 weeks postpartum: no complications	At 3 months: no complications	Between 1-3 years: no complications	At 6 months: no complications	At 8/9 months	At 24h after: no complications
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Table S3. Major reported AEs and related stimulation protocols in pediatric populations (Since 2017)

Study population, Number of subjects	Age range or mean age (years)	Montage; Electrode size	Intensity, Duration, # of sessions	AEs	Reference
Children with spastic hemiplegia cerebral palsy (n=10)	6-12	The anodal electrode was positioned on C3 or C4 (depending on the affected hemisphere) while the cathodal electrode was placed on the contralateral supra-orbital region (Fp1 or Fp2). Two carbon electrodes (5 x 5 cm and 7 x 5 cm) with sponge pads soaked in a salt solution were employed as the anode and cathode, respectively.	tDCS 1mA; 20min 1) anodal-tDCS-offline, 2) sham-tDCS-offline, 3) anodal-tDCS-online, and 4) ssham-tDCS-online, with a one-week interval	Participants reported no AEs and SEs related to tDCS but experienced the expected itching/needling sensation on the skin when the current was slowly increased to 1 mA.	(Farzamfar et al., 2024) https://pmc.ncbi.nlm.nih.gov/articles/PMC11520274/ (Farzamfar, Heirani, Amiri, Sedighi, & da Silva Machado, 2024)
Male adolescents with Autism Spectrum Disorder (n=22)	12-18 14.1 ± 1.9 years	Anodal tDCS: using 3.2 × 3.2 cm rectangular rubber electrodes and conductive Ten20 paste. The anode was placed at F3 and the cathode was over the right supraorbital region.	tDCS 2mA ,20 min; #10;	None mentioned	(Prillinger et al., 2023) DOI: 10.3390/jcm12175570 https://pubmed.ncbi.nlm.nih.gov/37685637/

<p>Children with radiologically confirmed perinatal brain bleed or stroke and resultant hemiparetic cerebral palsy (n=10)</p>	<p>10–19 15.2 ± 2.6</p>	<p>A bihemispheric tDCS montage targeted M1 using ipsilesional-anodal and contralesional-cathodal electrode positioning, Using 5 cm x 5 Soterix SNAPpads with inserted 42 mm medical conductive-rubber electrodes and 4 dissipation rivets were used</p>	<p>tDCS 1.5mA; 20 min; #5 home-based</p>	<p>No serious AEs (e.g., seizures), occurred during any session nor at 1-week follow-up.</p>	<p>(Christopher et al., 2023) DOI: 10.1016/j.brs.2023.08.024 https://pubmed.ncbi.nlm.nih.gov/37652136/</p>
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<p>Unmedicated children with ADHD (n=23)</p>	<p>6-12</p>	<p>tRNS: semi-dry 5 × 5 cm electrodes</p> <p>Electrode positions: right inferior frontal gyrus (rIFG) and left (IDL PFC).</p>	<p>tRNS 0.75 mA 20 min #10</p>	<p>Overall, there were 117 records of SEs reported during the trial, and none of them were considered clinically significant. The most common SEs were itching (27% and 33% of sessions in the active and sham groups, respectively), followed by discomfort (6% of sessions) and difficulty concentrating (5% of sessions). There were no significant between-group differences on all reported SEs ($p > 0.07$).</p>	<p>(Dakwar-Kawar et al., 2023)</p> <p>DOI:10.1038/s41398-023-02547-7</p> <p>https://pubmed.ncbi.nlm.nih.gov/37528107/</p>
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patients with ADHD or ASD (n=60) and healthy controls	6-17 and 18-45	The montages included: (1) anode over the motor cortex (C1) and cathode over the right frontopolar cortex above the eyebrow, (2) anode over the primary somatosensory cortex (P1) and cathode over the right frontopolar cortex above the eyebrow, (3) anode over the dorsolateral prefrontal cortex (DLPFC, F3) and cathode over the right frontopolar cortex above the eyebrow, (4) anode over the primary visual cortex (Oz) and cathode over (Cz) central midline, (5) anode over the temporal cortex (T3) and cathode over (T4) right temporal, (6) anode over the parietal cortex (P6–P8) and cathode over (Cz)	tDCS amplitude was randomly selected (0, 0.5, 1.0, and 2.0 mA); 10min; #2	no significant effect of low vs. high amperage on SE ratings from pre-to-post tDCS	(Buchanan et al., 2023) DOI: 10.3390/jcm12134346 https://pubmed.ncbi.nlm.nih.gov/37445385/ (Buchanan, Amare, Gaumond, D'Angiulli, & Robaey, 2023)
Children affected by chronic vegetative state, secondary to OHCA (n=3) Out-of-hospital cardiac arrest	1-3	constant current electrical stimulator by using saline-soaked surface sponge electrodes (5 × 7 cm). The anode was positioned over the left DLPF cortex (F3, according to the 10–20 international system while the cathode was placed over the contralateral shoulder	tDCS 2mA; 20min; #10	No SEs were reported	(Curatola et al., 2023) DOI: 10.1186/s13062-023-00379-5 https://pubmed.ncbi.nlm.nih.gov/37165387/
Hemiparetic Cerebral Palsy (n=1)	14 year old male	Anodal tDCS: At the right (contralesional) hemisphere. 5×5cm electrodes enclosed in 5×7cm sponges moistened in saline solution. The anode was placed on the TMS-derived motor hotspot of the right hemisphere and the cathode was placed on the forehead contralateral to the anode.	tDCS 1.5 mA 20 min tDCS #1	No major AEs occurred during the assessment, nor were reported at one-day follow-up	(Delatorre et al., 2023) DOI: 10.1080/17518423.2023.219 https://pubmed.ncbi.nlm.nih.gov/36967533/

participants with clinical presentation of hemiparesis with radiologic confirmation of stroke or other non-traumatic brain injury within the first year of life (n=14)	7-22 13.8 ± 3.63	tDCS was delivered with a Soterix 1 × 1 Limited Total Energy (LTE) device using 5 × 5 cm rubber electrodes housed in medical-grade 5 × 7 cm. The exact cortical location of the anode corresponded to the TMS-derived motor hotspot and was marked with a wax pen using stereotactic neuronavigation. The cathode was placed on the forehead contralateral to the anode.	tDCS 1.5mA; 20min	No SAEs occurred during the experimental procedures. Common minor AEs associated with non-invasive brain stimulation such as itchiness (real tDCS: 1/8, sham tDCS:= 1/6), tingling (real tDCS: 1/8), headache (sham tDCS: 1/6), and “unusual feelings on the head” (real tDCS: 1/8, sham tDCS:1/6) were minimal and resolved within the experimental session. Furthermore, no AEs were reported 24 hours after the session per parental report. Heart rate and blood pressure remained within normal physiologic ranges throughout the entire session.	(Nemanich et al., 2023) DOI: 10.1016/j.ejpn.2023.01.013 https://pubmed.ncbi.nlm.nih.gov/36878110/
Adolescent with severe traumatic brain injury (TBI) (n=1)	One adolescent (age unknown)	anodal tDCS prior to 16 physiotherapy sessions	tDCS 20 min #16, duration 4 weeks	itchiness under the electrodes during tDCS sessions	(Ryan et al., 2023) DOI: 10.1080/01942638.2022.2163214 https://pubmed.ncbi.nlm.nih.gov/36624962/
ADHD (n=69)	10-18	Anodal tDCS: Circular electrodes (Pistim; 3.14 cm ²) filled with EEG electrode gel were positioned using a head cap following the 10-10 system. For stimulation of the IDLPFC, anodal electrodes were positioned at AF3 and F3 (0.5 mA) and cathodal electrodes at TP7 and Oz (-0.5 mA). To stimulate the rIFG, anodal electrodes were positioned at F6 and F8 (0.5 mA) and cathodal electrodes at AFZ and P7 (-0.5 mA).	multichannel tDCS Total injected current strength of 1 mA; 20 min, #10	No serious AEs. Most frequent AE in both groups was headache (sham, n = 30; verum, n = 20), followed by nasopharyngitis (sham, n = 11; verum, n = 5) and feeling of electric discharge (sham, n = 5; verum, n = 3)	(Krauel et al., 2025) {Krauel, 2025 #39} DOI: 10.1001/jamanetworkopen.2024.60477 https://pubmed.ncbi.nlm.nih.gov/39982727/

children and adolescents with neuropsychiatric and neurodevelopmental disorders (n=92)	8-17	stimulation was delivered by a battery-operated stimulator (Brain-Stim stimulation by E.M.S. S.R.L-Bologna, Italy) using rectangular (i.e., tDCS experiments) or circular (i.e., tRNS experiment) 25 cm ² identical, saline-soaked, sponge electrodes	tDCS, and tRNS 1mA; 20min, #3	No participant reported serious AEs in any experiment (i.e., Experiment 1, Experiment 2, Experiment 3) and conditions (i.e., active and sham).	(Battisti et al., 2025) DOI: 10.1038/s41598-025-88256-1 https://pubmed.ncbi.nlm.nih.gov/39915614/
Adolescents suffering from Major Depressive Disorder (n=32)	10-18	The anode was placed at the left DLPFC, and the cathode at the right DLPFC.	tDCS 2mA; 20min; #10	No SAEs were observed during the study. Participants were found most likely to report SEs during the initial sessions, which generally diminished in subsequent sessions. Although most of the participants in the active group reported some SEs (13 out of 15), the majority of the sessions were found to be free of reported SEs (70 % out of 150 sessions), The most commonly reported SEs and AEs in the true group were burning (10 %), headache (6 %), numbness (4.6 %) and pain (4 %). But the severity of these effects remained limited to moderate.	(Upadhyay et al., 2025) DOI: 10.1016/j.ajp.2024.104349 https://pubmed.ncbi.nlm.nih.gov/39733498/

ADHD (n=15)	6-16	The anode was positioned on the left dorsolateral prefrontal cortex (F3 according to the 10–20 system for EEG), and the cathode in the supraorbital region was on the opposite side	tDCS 2mA; 30min; #5	AEs were mostly self-limiting and characterized as mild to moderate. Pruritus was identified in 9 (60%) children from the tDCS group and 3 (20%) from the sham-tDCS group. Tingling and burning of greater intensity were reported by 4 (26.7%) and 3 (20%) children, respectively, from the tDCS and sham-tDCS groups (Table 9).	(Guimarães et al., 2024) DOI: 10.3389/fpsyt.2023.1217407 https://pubmed.ncbi.nlm.nih.gov/38268562/ (Guimarães et al., 2023)
drug-naïve adolescents with OCD (n=18)	10-18	Two electrodes (size: 5 cm × 5 cm) were placed in the sponge (7 cm × 5 cm). The cathode was placed on the left SMA. an anode on the right deltoid	tDCS 2mA; 20min	No major AEs were recorded, and tDCS stimulation was well tolerated. 8 of 10 adolescents in active and 7 of 9 in the sham group reported at least one SE or AE (relative risk = 1.03, number needed to harm = 45.0). For an individual session, 53.3% of active stimulations and 51.4% of sham stimulations resulted in a SE. The maximum relative risk was for headache (2.14 for per session incidence and 1.56 for per individual incidence). Other AEs commonly reported were numbness, itching, pain at the stimulation site and sedation.	(Agrawal et al., 2024) DOI: 10.5409/wjcp.v13.i2.93138 https://pubmed.ncbi.nlm.nih.gov/38947993/
ASD (n= 97)	14-21 17.05 (2.48) tDCS 16.71 (2.04) sham	The cathode electrode (25 cm ²) and anode electrode (25 cm ²) were placed at positions “F3” and “F	tDCS 1.5mA; 20min; #10	No SAEs and prolonged AEs effects including epileptic seizures, skin lesions, and treatment-emergent mood episodes were reported.	(Han et al., 2023) DOI: 10.1177/13623613231169547 https://pubmed.ncbi.nlm.nih.gov/37151094/

Children with a Diagnosis of bilateral CP (n=5)	6-11 years mean age 8±1.8	The motor cortex contralateral to the chosen arm was then targeted. Current was delivered with a Soterix DC stimulator (Soterix, NYC) via 2 saline-soaked sponge electrodes with the anode placed over M1 and the cathode over the contralateral forehead, both held in place by a custom-sized headstrap. M1 location was approximated using the 10/20 EEG system to map targets of left (C3) or right (C4) (17	tDCS 1mA; 20min; #10	No serious AEs	(Raess et al., 2022) DOI: 10.3389/fresc.2022.843767 https://pubmed.ncbi.nlm.nih.gov/36188922/
ADHD (n=25)	10.83	The anode was placed on the scalp over the area of the DLPFC and cathode was placed on the scalp over the area of the vertex	tDCS 1mA; 20min; #12	Five SEs and AEs including tingling sensation, itching sensation, burning sensation, headache and scalp pain, were found to be statistically significant (in decreasing severity) when comparing pre/post scores over the 12 sessions. Overall, AEs were mild with no significant difference between groups. However, three children, all from the tDCS group, experienced headaches with two requiring temporary cessation and one requiring removal from the study.	(Schertz et al., 2022) DOI: 10.1016/j.jpsychires.2022.08.022 https://pubmed.ncbi.nlm.nih.gov/36174365/

children with hemiplegic cerebral palsy (n=30)	3-6	Two 5.5 × 4.0 cm electrodes were placed on the scalp with the anode positioned in the region over the M1 of the affected or more affected hemisphere according to the 10–20 electroencephalogram system, with the cathode electrode placed over the contralateral supraorbital area.	tDCS 1.5 mA; 20 min	No severe AE occurred among the 30 participants and only a few of them felt transient and slight discomfort (tingling, itching, burning sensation, dizziness, etc.).	(He et al., 2022) DOI: 10.3389/fnbeh.2022.925122 https://pubmed.ncbi.nlm.nih.gov/36160682/
ASD patients (n=7)	9-13	The cathode was placed over the right cerebellar hemisphere, 1 cm below and 4 cm lateral to theinion (corresponding to the cerebellar lobule VII on the scalp), and the anode was placed over the F3 position	tDCS 1mA; 20min; #20	No serious AEs were observed or reported. Three patients showed or reported a mild, temporary skin irritation at the site of stimulation.	(D'Urso et al., 2021) DOI: 10.3390/jcm11010143 https://pubmed.ncbi.nlm.nih.gov/35011884/
Adolescents With Autism Spectrum Disorder (n=20)	12-18	electrode montage with the anode over the left DLPFC (and the cathode over the right supraorbital region	tDCS 2mA; 20min; #10	no serious AEs or serious health risks for the participants of this study are expected.	(Prillinger et al., 2021) DOI: 10.3389/fpsy.2021.680525 https://pubmed.ncbi.nlm.nih.gov/34526918/
healthy children and adolescents and adults (n=43)	10-16 median 13.3 (n=15), 20-30 median 24.4 (n=28)	The motor cortex electrode was fixed over the area representing the right first dorsal interosseus (FDI) muscle as identified by TMS. The other electrode was fixed over the contralateral supraorbital area.	tACS: 1mA 20 Hz, 140 Hz and tRNS . 10 Min	Incidence and intensity did not differ between age groups for any side effect	(Splittgerber et al., 2020) https://pubmed.ncbi.nlm.nih.gov/32855633/
healthy children and adolescents (n=22)	10-18, mean age 15.18	anodal tDCS over the left dorsolateral prefrontal cortex. Five 3.14 cm ² circular PiStim electrodes, filled with EEG electrode gel. Electrodes were positioned using a head cap following the 10–10 system Anodal electrodes: F3, AF3, AF7 Reference electrodes: T7, Fp2	tDCS: 2 mA, 20 min #4	The intensity of perceived itching during stimulation was significantly higher under anodal compared to sham stimulation	(Splittgerber et al., 2021) DOI: 10.1038/s41598-021-00933-z https://pubmed.ncbi.nlm.nih.gov/34728684/

Autism (n=50)	4-14	Two anodal electrodes were placed over the left FC1 and right FC2, while the two cathode electrodes were placed over the left and right supraorbital areas. The anode and cathode electrodes had surface areas of 8 cm ²	tDCS 1mA; 20min; #10	Overall, the tDCS intervention was well tolerated during the stimulation sessions, and no AEs were reported.	(Hadoush et al., 2020) DOI: 10.1002/aur.2290 https://pubmed.ncbi.nlm.nih.gov/32149480/
Healthy participants (n=24)	12-18	The active electrode (anode) centered over the right M1 and the cathode over the contralateral supraorbital area 25cm ²	tDCS 1mA; 20min	A total of 120 tDCS sessions were performed without any complications or serious AEs. The most common reported sensation was itching (56%) ranging from mild (75%) to moderate (25%)	(Cole et al., 2018) DOI: 10.3389/fnins.2018.00787 https://pubmed.ncbi.nlm.nih.gov/30429768/
right-handed dyslexics (n=26)	13.6	anodal electrode over the left parieto-temporal regions on the site that corresponds to midway between P7 and TP7, cathodal electrode on the right side of the parieto-temporal regions, which was chosen to exclude brain regions that are typically engaged in reading processes, such as the frontal and occipital cortices, 5x5cm	tDCS 1mA; 20min	No participant asked to withdraw from the study or reported significant discomfort at the electrode sites. The main AEs for all 468 stimulation sessions were tingling and itching, which subsided rapidly due to habituation (3 active and 2 sham participants); burning sensation (4 active and 1 sham participant); and local redness (2 active participants). None of the participants reported discomfort or AES at any post-treatment time point	(Costanzo et al., 2019) DOI: 10.1016/j.neuropsychologia.2018.03.016 https://pubmed.ncbi.nlm.nih.gov/29550525/
child suffering from early onset epileptic encephalopathy (n=1)	30 months	HD-tDCS in reducing epileptiform activity in a 30-month-old child	HD-tDCS .10 intervention days spanning two weeks including pre- and post-intervention video-EEG monitoring	There were no serious AEs or SEs related to the HD-tDCS intervention.	(Meiron et al., 2018) DOI: 10.1080/02699052.2017.1390254 https://pubmed.ncbi.nlm.nih.gov/29156988/

Developmental dyslexia (n=29)	8-17 median 11.59	Two 5 × 7 cm rubber electrodes in 0.9% saline-soaked sponges were placed horizontally over T7 and T8. The reference electrode was placed on the nose-tip, the ground at AFz	tACS: 1 mA, 40 HZ, 20 min 40 min #10	None of the participants reported discomfort or AEs at any stimulation session or at any post-intervention time-point	(Rufener, Zaehle, & Krauel, 2023) DOI: 10.1016/j.dcn.2023.101317 https://pubmed.ncbi.nlm.nih.gov/37898018/
children with language delay (n = 94)	2-6	tDCS: electrode size of 5 × 7 cm. The anode stimulated the temporal lobe centered on the left Wernicke's area, and the cathode was placed on the right scapula	1mA, 20min, #20	No SAEs, such as epilepsy, headaches, or abnormal behavior were reported, and no skin burning, redness, or swelling was observed. Skin flushing occurred at the electrode application site after tDCS treatment and subsided after a few minutes. Five children (three in the comprehensive group and two in the tDCS group) reported discomfort at the beginning of the tDCS treatment, which resolved spontaneously after a few seconds.	(Zhou et al., 2024) DOI: 10.3389/fneur.2024.1412959 https://pubmed.ncbi.nlm.nih.gov/39070055/
Children with perinatal stroke and hemiparetic cerebral palsy (n=23)	6-18, mean 11.8	Cathodal tDCS over the contralesional primary motor cortex (M1). Anode was placed over the contralateral forehead. 2 saline-soaked sponge electrodes (25 cm ²).	1mA, 20 min #10	No serious AEs. The most common SE was itching (39%) that was mild (7) or moderate (2), decreased over sessions, and was comparable between treatment groups (p = 0.67). SEs and AEs included headache (3), mild burning (3), or unpleasant tingling (1). Participants could not predict whether they received active or sham tDCS (48% guessed correctly).	(Kirton et al., 2017) DOI: 10.1212/WNL.0000000000003518 https://pubmed.ncbi.nlm.nih.gov/27927938/

healthy school-aged children	School aged children	<p>Two 25 cm² saline-soaked sponge electrodes were applied to the scalp and held in place by a commercially available light plastic “headband” system. The active electrode was placed over the respective primary motor cortex while the reference electrode was placed over the contralateral forehead.</p> <p>2) Anodal tDCS on the right (contralateral) hemisphere. The anode was centered over the right M1 with the cathode over the contralateral supraorbital area.</p> <p>3) Cathodal tDCS on the left (ipsilateral) hemisphere. The cathode was centered over the left M1 with the anode over the contralateral supraorbital area.</p> <p>4) Cathodal tDCS on the left hemisphere. The cathode was centered over the left M1 with the anode over the contralateral supraorbital area.</p>	<p>20 min #3</p> <p>2) 1mA 3)1mA 4)2mA</p>	<p>There were no serious AEs. The most commonly reported sensation was itching under the site of the anode (44%). The proportion did not differ between treatment groups. Younger children (< 11 years) were more likely to rank the intensity of itching as moderate or severe, rather than mild (33 vs 14%). Additional sensations included: mild burning (7%) or unpleasant tingling (6%) under the site of the electrode. Headache was reported in 1 session of sham tDCS. In all sham tDCS sessions, any sensations faded within 5 min of stimulation. Sensations reported with active tDCS persisted for the duration of the stimulation in 40% of anodal and 77% of cathodal tDCS sessions, with no difference between stimulation intensities. There were no significant differences between the tolerability of sham, 1 mA or 2 mA tDCS.</p>	<p>(Ciechanski & Kirton, 2016)</p> <p>DOI: 10.1093/cercor/bhw114</p> <p>https://pubmed.ncbi.nlm.nih.gov/27166171/</p>
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<p>Children with drug resisted refractory epilepsy (n=12)</p>	<p>3-17</p>	<p>Cathodal tDCS: Square surface electrodes (25 cm²) coated with EEG electrode gel were used. The cathodes were applied over one or two EEG sites (international 10–20 system) with the most frequent epileptiform activity seen in ictal and interictal EEG recordings. Anodes were positioned over the ipsilateral or contralateral supra-orbital region of the forehead depending on comfort and accessibility during EEG recording.</p>	<p>20 min # 3 or 4 <10 years: 0.8 mA >10: 1 mA</p>	<p>One child (case 7) had a seizure before the first day of tDCS and a seizure before and after the last day of tDCS (based on the vEEG recording). This was not unexpected as he had been having innumerable daily seizures at that time, and the seizure semiology was the same. None of the other children had any significant AEs during or after tDCS. Four children had mild irritation or itchiness during the stimulation, three reported a mild transient headache after the stimulation, and one child said he felt slightly wobbly on his feet for a few minutes after the stimulation.</p>	<p>(Ghosh & Nagarajan, 2023) DOI: 10.3390/brainsci13050760 https://pubmed.ncbi.nlm.nih.gov/37239232/</p>
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<p>Adolescents with ADHD (n=15)</p>	<p>12-16 Mean 14.2</p>	<p>Anodal tDCS over the left DLPC. Applied via a pair of rubber electrodes (round anode with a surface area of 314 mm² and a rectangular cathode with a surface area of 1250 mm²).</p>	<p>1mA, 20 min #5</p>	<p>A mild tingling and itching sensation under the electrodes was the most commonly reported SEs. This sensation was reported by 46% of the subjects during anodal tDCS and by 46% during sham stimulation. None of the subjects reported fatigue, burning, pain, or other uncomfortable sensations during tDCS or sham stimulation. Furthermore, none found the stimulation procedure to be unpleasant nor were any difficulties reported in concentrating during neuropsychological assessment. Headache after anodal stimulation was reported only by one subject. None of the participants reported changes in visual perception or were more hyperactive during or after the stimulation.</p>	<p>(Soff et al., 2017) DOI: 10.1007/s00702-016-1646-y https://pubmed.ncbi.nlm.nih.gov/27853926/</p>
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children with cerebral palsy (n=8) 10 participants during the primary visit, 8 at the 6-month visit, and 8 at the 12-month visits.	6-18	6 and 12 month after treatment	1,5 mA, 20 min. 5 consecutive days of remotely instructed tDCS	In the Subject Report of Symptom survey, there were 8 reported symptoms that were reported at the 6- or 12-month visit that were not reported at baseline or increased in severity since baseline. These symptoms include dizziness (n=1), abnormal sleep (n=2), difficulty paying attention (n=1), anxious, worried or nervous (n=1), and sleepiness (n=3). All 8 of these reported symptoms were deemed not related to stimulation by our medical monitor. Of the 8 reported symptoms, 2 of them were absent when asked again at the 12-month visit. There were also 4 reported symptoms that decreased in severity from baseline.	(Lench et al., 2024) DOI: 10.1016/j.brs.2024.04.017 https://pubmed.ncbi.nlm.nih.gov/38740181/
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Table S4. Summary of studies of tES (tDCS, tACS) in healthy older adults.

tDCS							
N	Mean age/age range (years)	Anode position; size (cm ²)	Cathode position; size (cm ²)	Current (mA)	Duration (min); # of sessions	AEs	References

n = 37 ACTIVE n = 18 SHAM n=19	61 ± 6	left M1 hand; 45cm2	Contralateral supraorbital ; 45cm2	2.0	20; 5x	na	(Dumel et al., 2018)
n=378 ACTIVE (n = 190) SHAM (n = 188)	71.5+-5.1	F4; 35cm2	F3; 35cm2	2.0	20; 20x	Ratings of any sensation on a 10-point scale. All ratings were largely between 0 and 1, with the active group showing significantly lower pain but greater tingling and burning sensation than the sham group.	(Hausman et al., 2024)
n = 30 ACTIVE (n = 15) SHAM (n = 15)	55-70	left right C2 dermatomes; 35cm2	left right C2 dermatomes; 35cm2	1.5	12.5; 1x	Associative memory; AEs measured with questionnaire (reporting only figure, no numbers); no major AEs	(Luckey et al., 2020)
n = 18 ACTIVE (n = 9) SHAM (n = 9)	82±4	F3; 35cm2	Fp2; 35cm2	2.0	20; 10x	mild sensations under the electrode (65%), skin redness (32%), and sleepiness (30%).	(Manor et al., 2018)
ACTIVE (n = 35) SHAM (n = 33)	66.7	F3; 35cm2	Fp2; 35cm2	1.5	15; 15x	all assessed SEs and AEs (e.g., itchiness, burning sensation, pain, headache, anxiety, difficulty in concentration) were not significantly different between the tDCS and sham. Raw numbers not reported	
ACTIVE (n = 168) SHAM (n = 166)	71.5 ± 5.1	F4; 35cm2	F3; 35cm2	2.0	20; 20x	average ratings for each sensation were largely between 0 and 1 on a 10-point scale. At each assessment visit, participants were asked to report any AEs and changes in medical conditions or medication use since their last visit. All AEs were regularly reviewed by an external Data Safety Monitoring Board. (Table 7) AEs (no serious): Overall 144 (43.1%) - serious AEs : overall 35 (10.5%) (not clear what they measured, participants were asked to report any AEs and changes in medical conditions or medication use since their last visit.)	(Hausman et al., 2023)
hd-tDCS							

N	Mean age/age range (years)	Anode electrode position; size (cm2)	Cathode electrode position; size (cm2)	Current (mA)	Duration (min); # of sessions	AEs	References
n=6	88.8-5.0	left dlpc; cm2	N/R; cm2	1.5	20; 10x	2 out of 6 (33.3%) participants reported some type of SEs across their stimulation sessions. Sensations under electrodes were reported in 12.1% of the sessions, and skin redness was noticed in 2.4% of the sessions.	(Lo et al., 2023)
tACS							
N	Mean age/age range (years)	Anode electrode position; size (cm2)	Cathode electrode position; size (cm2)	Current (mA)	Duration (min); # of sessions	AEs	References
Exp1 (n = 42) Exp2 (n = 28)	68.8 ± 4.4 (exp 1) 69.6 ± 3.7 (exp 2)	HD-tACS; 1.13cm2	HD-tACS; 1.13cm2	1.6 mA fronto-temporal montage 1.0 mA temporal montage 0.6 mA frontal montage 8-Hz (or individual theta)	25; 1x	After each test day, we administered a safety questionnaire and visual analog scale, which included questions regarding attention, concentration, mood, vision, headache, fatigue, and skin sensations under the stimulating electrodes. Scores on these ratings did not significantly differ by stimulation condition	(Reinhart & Nguyen, 2019)

Table S5 TES combined with other non-pharmacological interventions

Behavioural intervention											
N	Mean age; age sd/range (years)	Anode electrode position; size (cm2)	Cathode electrode position; size (cm2)	Current (mA)	Duration (min); # of sessions	NIBS	Online /Offline	Combined Intervention	AEs	BLINDING	References
n=35 (ACTIVE n = 18 SHAM n = 17)	34.17 (2.14)	Fpz; 1	AF7, AF8, F3, F4, Fz; 1	1.5	20; x1	hd-tDCS	offline	extinction training	tDCS Adverse Effects Questionnaire (tDCS-AEQ) assesses the presence of ten common tDCS side effects rated on a scale from zero (absent) to three (severe). Not reported	effective	Adams et al., 2023
n = 84 SHAM F8 anodal (N = 17) SHAM F7 anodal (N = 17) ACTIVE F8 anodal (N = 26) ACTIVEF7 anodal (N = 24)	24.19 (4.02)	F7,F8;16	F7,F8;16	1.5	20;x1	tDCS	Online	fear extinction	nr	nr	Dittert et al., 2018

n = 43										only mild AEs.		
ACTIVE n = 27	20.42 (4.99)	contralateral deltoid; 24.75	F4; 24.75	1	20; x1	tDCS	Offline	fear conditioning paradigm	Mostly itching (5/43), tingling (10/43), somnolence (9/43), skin redness (5), headache (3/43)	nr	Ganho-Ávila et al., 2019	
SHAM n=16												
n = 34												
tDCS n = 16 CONTROL n = 18	23.32 (5.67)	contralateral deltoid; 25	F4; 25	1	20; x1	tDCS	Offline	fear conditioning paradigm	only mild AEs	na	Ganho-Ávila et al., 2022	
180	23.8 (2.3)	midpoint of FC5 and FT7 // return electrodes were placed over AF7, CP5, and FC3	midpoint of FC5 and FT7 // return electrodes were placed over AF7, CP5, and FC3		10; x1	tDCS	Online	Fear extinction paradigm	not significant compared to sham	effective	Ma et al., 2024	
Cognitive training												

n = 27	29.04 (5.77)	F3; 25 right bicep; 51	right bicep; 51 F3; 25	2	30; x3	tDCS	Online	cognitive tasks	The most common reported symptom was tingling (n = 11) followed by itching (n = 8). The highest rated severity for both of these symptoms was a three (on a scale from 1 to 10). No serious AEs reported	effective	Duffy et al., 2024
n = 38 DLPFC group n = 19 Fronto-medial FM group n = 19	23.82 (3.56)	F3; 35 (anodal DLPFC) AFz; 35 (anodal fronto-medial)	contralateral supraorbital; 35 (anodal DLPFC) Pz; 35 (anodal fronto-medial)	2	20; x3	tDCS	online	flanker go/no-go task	All participants completed the tDCS sessions without major complaints. Participants receiving sham, anodal, and cathodal tDCS in different montages were comparable regarding headache, neck pain, scalp pain, tingling, burning	nr	Holczer et al., 2023

74	22.14 (3.38)	T7 (16cm ²)	T8 (16cm ²)	2	11; x1	tACS	Online	Memory tasks	A more prominent reported auditory discomfort during both 40 Hz-rAS and 60 Hz-rAS stimulation compared to control and a more pronounced headache during 40 Hz-rAS compared with control. The tACS group reported more prominent phosphenes during both the 40 Hz and 60 Hz-tACS compared with the control, more pronounced pain during the 40 Hz-tACS compared with the control and more pronounced fatigue during the 40 Hz-tACS compared with the 60 Hz-tACS.	nr	Manippa et al., 2024
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Exp1 (n = 42)	68.8 (4.4)(exp 1)	; 1.13	; 1.13	1.6 mA fronto-temporal montage	25; x1	hd-tACS	Offline	After each test day, we administered a safety questionnaire and visual analog scale, which included questions regarding attention, concentration, mood, vision, headache, fatigue, and skin sensations under the stimulating electrodes. Scores on these ratings did not significantly differ by stimulation condition	Reinhart & Nguyen, 2019
Exp2 (n = 28)	69.6 (3.7)(exp 2)			1.0 mA temporal montage 0.6 mA frontal montage 8-Hz (or individual theta) peak-to-peak					

ACTIVE (n = 35)	66.7 (-)	F3; 35cm2	Fp2; 35cm2	1.5	15; 15x	tDCS	online	Executive Function training, a mixed of various tasks	all assessed side effects on a scale from 0 to 5 (e.g., itchiness, burning sensation, pain, headache, anxiety, difficulty in concentration) were not significantly different between the tDCS and sham	nr	Yu et al, 2020
SHAM (n = 33)									raw numbers not reported		
n=90 ACTIVE + CT n =30 SHAM + CT n = 30 ACTIVE only n = 30	23.8 (2.3)	F4; 35	left cheek; 35	2	20; x12	tDCS	Offline	adaptive dual n back	Each time the tDCS device was used, the participants were asked whether they felt unwell and whether they intended to continue the experiment.	nr	Zhu et al, 2025
Motor learning											
n = 37 ACTIVE n = 18	61 (6)	left M1 hand; 45	Contralateral supraorbital ; 45cm2	2	20; 5x	tDCS	Online	motor sequence learning	nr	nr	Dumel et al, 2018



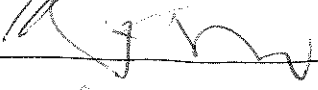
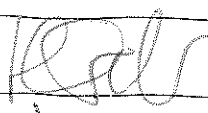
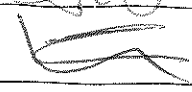

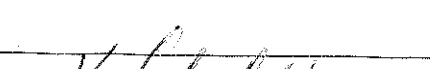

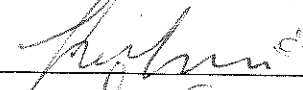
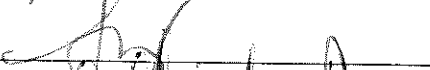

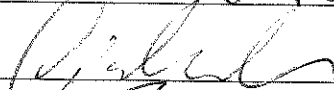
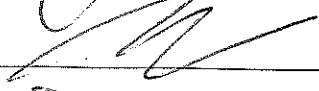



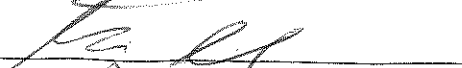

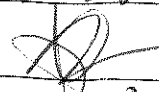



SHAM n=19												
108	24.2 (6.12)	P4, CP4, CP2, and P2; 2.7	F4, F2, AF4, and Fz; 2.7	4	12; x1	hd- tDCS	online	motor learning sequence	The post- stimulation questionnaire records at most, moderate sensation levels at the beginning of the stimulation (Fig. 7). Sensation decreases afterwards, subsiding to very mild levels by the end of the trial. Bayes Factor analysis shows that there were no significant differences in sensation ratings between the anodal and cathodal groups.	effective	Hsu et al, 2023	
anodal (N = 36) cathodal (N = 36) tDCS sham (N = 36)												
Physical training												

n = 12	29.4 (7.3)	<p>HD-tDCS: Cz,C1,C2,</p> <p>conventional tDCS:C1,Cz,C2,Cp1, Cpz, Cp2</p> <p>active SHAM: Cz,C1,C2,</p> <p>1.2 cm ring electrodes</p>	<p>HD-tDCS: FC1, FC2, C3,C4, P1,P2</p> <p>conventional tDCS: PO3, POz, PO4</p> <p>active SHAM: FC1, FC2, C3, C4, P1, P2</p>	<p>HD-tDCS: 2.4</p> <p>conventional tDCS: 2</p> <p>active SHAM: 2</p>	20; x1	hd-tDCS / tDCS	Offline	time to exhaustion	<p>tDCS was well-tolerated with no side or AEs being reported. The most common sensations reported were itching, burning sensation, heating, and pitching that was felt on the head starting at the beginning or middle of the stimulation with varying duration. All subjects reported these sensations did not affect their performance in any tDCS condition.</p>	effective	da Silva Machado et al., 2021
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n = 6	88.8 (5.0)	left DLPFC; nr	nr; nr	1.5	20; x10	hd- tDCS	Offline	physical therapy	There were no unanticipated side effects or AEs. 33.3% participants reported some type of side effects across their stimulation sessions. Sensations under electrodes were reported in 12.1% of the sessions, and skin redness was noticed in 2.4% of the sessions.	effective	Lo et al., 2023
n = 115 (assigned to different groups; of this 91 received either active or sham stimulation)	25.24; 2.03	F3; 3.14 Fz,FC1,FC5,AF7; 3.14	F3; 3.14 Fz,FC1,FC5,AF7; 3.14	1	25; x1	hd- tDCS	Online/Offline	aerobic exercise + inhibition task	nr	nr	Thomas et al. 2021
Virtual reality											

n = 28 (ACTIVE n = 11 SHAM n = 14)	37.56 (16.92)	Fpz; 3.14	chin; 25	1	20; x2	tDCS	online	height exposure through virtual reality exposure therapy (VRET)	No significant AEs were reported (by participants or experimenters). Two subjects could not attend the last VRET session for personal organizational reasons, and one preferred not to complete the protocol due to apprehension of having a headache. Two dropouts occurred in the active group, and there was one dropout in the sham group.	nr	Bulteau et al., 2022
n = 22	25.2 (2.59)	C3;25	CONTRALATERAL SUPRAORBITAL;25	1	20;x1	tDCS	Online	motor skill learning in surgical procedural	No participants dropped out at any phase of the study	effective	Ciechanski et al., 2017

ALL AUTHORS MUST SIGN

SEHUMMANN		Date: 12/06/2025
Floel		Date: 12/06/2025
PADBERG		Date: 12/06/2025
HARTWIG	SIEMER 	Date: 12/06/2025
Friedhelm	Hummel 	Date: 12/06/2025
SARA ASSECONDI	Sara Asseconi 	Date: 12/06/2025
Ulf Hermann		Date: 12/06/2025
Klaus Scheuermann	K. Schellhorn 	Date: 12/06/2025
Jovana Bogelic		Date: 12/06/2025
Ana Branco		Date: 12/06/2025
PRIMO ALBERTO	Alberto Pri 	Date: 12/6/2025
Lukas Diedrich		Date: 12/6/2025
Marek Bilsa		Date: 12/6/2025
Ro, Cohen Kadosh		Date: 12/6/2025
BABUEN CHRIS		Date: 12/6/2025
Bergmann, Tilok		Date: 12/6/2025
Nikander, Mika		Date: 12/6/2025
Thielscher, Axel		Date: 12/6/2025
Wisniewski, Miles		Date: 12/6/2025
Oitz, Alexander		Date: 12/6/2025
LEFAUCHEUR, Jean-Pascal		Date: 12/6/2025
D'URSO GIORGIO		Date: 12/6/2025

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