DIGITALIZED TRANSCRANIAL ELECTRICAL STIMULATION: A CONSENSUS STATEMENT

Andre R Brunoni [a,b,c] Hamed Ekhtiari[d], Andrea Antal[e], Paradee Auvichayapat[f], Chris Baeken [g,h,i,j] Isabela M. Benseñor [k] , Marom Bikson[l], Paulo Boggio[m], Barbara Borroni[n], Filippo Brighina [o], Jerome Brunelin [p,q], Sandra Carvalho[r], Wolnei Caumo [s,t,u,v], Patrick Ciechanski[w], Leigh Charvet[x], Vincent P. Clark [y], Roi Cohen Kadosh[z], Maria Cotelli[aa], Abhishek Datta[ab], Zhi-De Deng [ac], Rudi De Raedt[ad], Dirk De Ridder[ae], Paul B. Fitzgerald[af], Agnes Floel [ag,ah], Flavio Frohlich [ai,aj,ak,al,am,an], Mark S. George [ao,ap], Peyman Ghobadi-Azbari [aq, ar], Stephan Goerigk [as,at,au], Roy H. Hamilton[av], Shapour J. Jaberzadeh[aw], Kate Hoy[af], Dawson J. Kidgell[ax], Arash Khojasteh Zonoozi [aq,ay], Adam Kirton[az], Steven Laureys[ba], Michal Lavidor[bb], Kiwon Lee[bc] , Jorge Leite[bd], Sarah H. Lisanby[be], Colleen Loo[bf,bg], Donel M. Martin[bf,bg], Carlo Miniussi[bh], Marine Mondino [o,p], Katia Monte-Silva[bi,bj], Leon Morales-Quezada[bk], Michael A. Nitsche[bl,bm], Alexandre H. Okano[bj,bn,bo], Claudia S. Oliveira[bp,bq], Balder Onarheim[br], Kevin Pacheco-Barrios [bs,bt], Frank Padberg[bu], Ester M. Nakamura-Palacios[bv] , Ulrich Palm [bw,bx], Walter Paulus[by], Christian Plewnia[bz], Alberto Priori[ca], Tarek K. Rajji [cb,cc,cd], Lais B. Razza[ce], Erik M. Rehn[cf], Giulio Ruffini[cg], Klaus Schellhorn[ch], Mehran Zare-Bidoky[aq,ci], Marcel Simis[cj], Pawel Skorupinski[ck], Paulo Suen [ce], Aurore Thibaut[cl], Leandro C.L. Valiengo[c], Marie-Anne Vanderhasselt[h,i], Sven Vanneste[cm], Ganesan Venkatasubramanian[cn], Ines R. Violante[co], Anna Wexler[cp], Adam J. Woods[cq,cr,cs], Felipe Fregni[bs]

[a]Department and Institute of Psychiatry, Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil

[b]Department of Internal Medicine, Faculdade de Medicina da Universidade de Sao Paulo & Hospital Universitário, Universidade de Sao Paulo, São Paulo, Brazil

[c]Laboratory of Neurosciences (LIM-27), Instituto Nacional de Biomarcadores em Neuropsiquiatria (INBioN), Service of Interdisciplinary Neuromodulation (SIN), Department and Institute of Psychiatry, Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil

[d]Laureate Institute for Brain Research (LIBR), Tulsa, OK, USA

[e]Department of Neurology, University Medical Center Gottingen, Gottingen, Germany

[f]Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

[g]Vrije Universiteit Brussel (VUB): Department of Psychiatry University Hospital (UZBrussel), Brussels, Belgium

[h] Department of Head and Skin, Ghent University Hospital, Ghent University, Ghent, Belgium

[i]Ghent Experimental Psychiatry (GHEP) Lab, Ghent, Belgium

[j]Eindhoven University of Technology, Department of Electrical Engineering, the Netherlands

[k]Center for Clinical and Epidemiological Research, University of São Paulo, São Paulo, Brazil

[l]The Department of Biomedical Engineering, The City College of New York, The City University of New York, NY, USA

[m]Social and Cognitive Neuroscience Laboratory, Center for Biological Science and Health, Mackenzie Presbyterian University, São Paulo, Brazil

[n]Centre for Neurodegenerative Disorders, Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Italy

[o]Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D.), University of Palermo, Palermo, Italy

[p]Centre Hospitalier le Vinatier, Bron, France

[q]INSERM Ul 028, CNRS UMR 5292, PSYR2 Team, Centre de recherche en Neurosciences de Lyon (CRNL), Université Lyon 1, Lyon, France

[r]Translational Neuropsychology Lab, Department of Education and Psychology and William James Center for Research (VvJCR), University of Aveiro, Campus Universitário de Santiago, Aveiro, Portugal

[s]Post-Graduate Program in Medical Sciences, School of Medicine, Universidade Federal do Rio Grande do Sul (UFRGS), Brazil

[t]Laboratory of Pain and Neuromodulation at Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brazil

[u]Pain and Palliative Care Service at HCPA, Brazil

[v]Department of Surgery, School of Medicine, UFRGS, Brazil

[w]Faculty of Medicine and Dentistry, University of Alberta, 1-002 Katz Group Centre for Pharmacy and Health Research, Edmonton, Alberta, Canada

[x]Department of Neurology, NYU Grossman School of Medicine, New York, NY, USA

[y]Psychology Clinical Neuroscience Center, Department of Psychology, The University of New Mexico, Albuquerque, NM, USA

[z]School of Psychology, Faculty of Health and Medical Sciences, University of Surrey, Guilaford, UK

[aa]Neuropsychology Unit, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy

[ab]Research and Development, Soterix Medical Inc., New York, USA

[ac]Noninvasive Neuromodulation Unit, Experimental Therapeutics & Pathophysiology Branch, National Institute of Mental Health, Bethesda, MD, USA

[ad]Department of Experimental Clinical and Health Psychology, Ghent University, Belgium

[ae]Section of Neurosurgery, Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

[af]Epworth Centre for Innovation in Mental Health, Epworth Healthcare and Monash University Department of Psychiatry, Camberwell, Victoria, Australia

[ag]Department of Neurology, University Medicine Greifswald, Greifswald, Germany

[ah]German Center for Neurodegenerative Diseases (DZNE), Rostock/Greifswald, Germany

[ai]Department of Psychiatry, University of North Carolina, Chapel Hill, NC, USA

[aj]Carolina Center for Neurostimulation, University of North Carolina, Chapel Hill, NC, USA

[ak]Neuroscience Center, University of North Carolina, Chapel Hill, NC, USA

[al]Department of Cell Biology and Physiology, University of North Carolina, Chapel Hill, NC, USA

[am]Department of Biomedical Engineering, University of North Carolina, Chapel Hill, NC, USA

[an]Department of Neurology, University of North Carolina, Chapel Hill, NC, USA

[ao]Department of Psychiatry, Medical University of South Carolina, Charleston, SC, USA

[ap]Ralph H. Johnson VA Medical Center, Charleston, SC, USA

[aq]Iranian National Center for Addiction Studies, Tehran University of Medical Sciences, Tehran, Iran

[ar]Department of Biomedical Engineering, Shahed University, Tehran, Iran

[as]Department of Psychiatry and Psychotherapy, LMU Hospital, Munich, Germany

[at]Department of Psychological Methodology and Assessment, LMU, Munich, Germany

[au]Hochschule Fresenius, University of Applied Sciences, Munich, Germany

[av]Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA

[aw]Department of Physiotherapy, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Australia

[ax]Department of Physiotherapy, School of Primary and Allied Health Care, Faculty of Medicine, Nursing and Health Science, Monash University, Melbourne, Australia

[ay]Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[az]Department of Clinical Neurosciences and Department of Pediatrics, University of Calgary, Calgary, Alberta, Canada

[ba]Coma Science Group, GIGA-Consciousness, GIGA Institute, University of Liège, Liege, Belgium

[bb]Bar Ilan University, Department of Psychology, and the Gonda Brain Research Center, Israel

[bc]Ybrain Corporation, Gyeonggi-do, Republic of Korea

[bd]INPP, Portucalense University, Porto, Portugal

[be]Noninvasive Neuromodulation Unit, Experimental Therapeutics & Pathophysiology Branch, National Institute of Mental Health, Bethesda, MD, USA

[bf]School of Psychiatry, University of New South Wales, Sydney, NSW, Australia

[bg]Black Dog Institute, Sydney, NSW, Australia

[bh] Center for Mind/Brain Sciences - CIMeC, University of Trento, Rovereto, Italy

[bi]Applied Neuroscience Laboratory, Department of Physical Therapy, Universidade Federal de Pernambuco, UFPE, Recife, PE, Brazil

[bj]NAPeN Network (Núcleo de Assistência e Pesquisa em Neuromodulação), Brazil

[bk]Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA 02215, USA

[bl] Department of Psychology and Neurosciences, Leibniz Research Centre for Working Environment and Human Factors, Dortmund, Germany

[bm]Department of Neurology, University Medical Hospital Bergmannsheil, Bochum, Germany

[bn] Center for Mathematics, Computation, and Cognition, Universidade Federal do ABC, São Bernardo do Campo, Brazil

[bo] Brazilian Institute of Neuroscience and Neurotechnology (BRAINN/CEPID-FAPESP), University of Campinas, Campinas, São Paulo, Brazil

[bp] Master's and Doctoral Program in Health Sciences, Faculty of Medical Sciences, Santa Casa de Sao Paulo, Sao Paulo, Brazil

[bq] Master's and Doctoral Program in Human Movement and Rehabilitation, Evangelical University of Goiás, Anápolis, Brazil

[br] PlatoScience ApS, Copenhagen, Denmark

[bs] Neuromodulation Center and Center for Clinical Research Learning, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

[bt] Universidad San Ignacio de Loyola, Vicerrectorado de Investigación, Unidad de Investigación para la Generacion y Sintesis de Evidencias en Salud, Lima, Peru

[bu] Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany

[bv] Laboratory of Cognitive Sciences and Neuropsychopharmacology, Program of Post-Graduation in Physiological Sciences, Health Sciences Center, Federal University of Espirito Santo, Vitória, ES, Brazil

[bw] Department of Psychiatry and Psychotherapy, Klinikum der Universität München, Munich, Germany

[bx] Medical Park Chiemseeblick, Rasthausstr. 25, 83233 Bernau-Felden, Germany

[by] Department of Neurology. Ludwig Maximilians University Munich, Klinikum Großhadern, Marchioninistr, München, Germany

[bz] Department of Psychiatry and Psychotherapy, Tübingen Center for Mental Health (TüCMH), Neurophysiology and Interventional Neuropsychiatry, University of Tübingen, Tübingen, Germany

[ca] Aldo Ravelli Research Center for Neurotechnology and Experimental Neurotherapeutics, Department of Health Sciences, University of Milan, Milan, Italy

[cb] Centre for Addiction and Mental Health, Toronto, Canada

[cc] Temerty Faculty of Medicine, University of Toronto, Toronto, Canada

[cd] Toronto Dementia Research Alliance, Toronto, Canada

[ce] Service of Interdisciplinary Neuromodulation (SIN), Department and Institute of Psychiatry, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

[cf] Flow Neuroscience, Malmo, Skane Lan, Sweden

[gs] Neuroelectrics Corporation, Cambridge, MA, USA

[ch] neuroConn GmbH, Ilmenau, Germany

[ci] School of Medicine, Shahid-Sadoughi University of Medical Sciences, Yazd, Iran

[cj] Physical and Rehabilitation Medicine Institute, General Hospital, Medical School of the University of São Paulo, Sao Paulo, Brazil

[ck] Neuroelectrics Corporation, Cambridge, MA, USA

[cl] Coma Science Group, GIGA-Consciousness & Centre du Cerveau, University and University Hospital of Liège, Liège, Belgium

[cm] Lab for Clinical & Integrative Neuroscience, Trinity College of Neuroscience, Trinity College Dublin, Ireland

[cn] Department of Psychiatry, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru, India

[co] School of Psychology, Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK

[cp] Department of Medical Ethics and Health Policy, University of Pennsylvania, Philadelphia, PA, USA

[cq] Center for Cognitive Aging and Memory, McKnight Brain Institute, University of Florida, Gainesville, FL, USA

[cr] Department of Clinical and Health Psychology, University of Florida, Gainesville, FL, USA

[cs] Department of Neuroscience, University of Florida, Gainesville, FL, USA

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Mobile Health ; Non-Invasive neuromodulation ; Digital health ; Systematic review ; Delphi panel

ABSTRACT

Objective: Although relatively costly and non-scalable, non-invasive neuromodulation interventions are treatment alternatives for neuropsychiatrie disorders. The recent developments of highly-deployable transcranial electric stimulation (tES) systems, combined with mobile-Health technologies, could be incorporated in digital trials to overcome methodological barriers and increase equity of access. The study aims are to discuss the implementation of tES digital trials by performing a systematic scoping review and strategic process mapping, evaluate methodological aspects of tES digital trial designs, and provide Delphi-based recommendations for implementing digital trials using tES.

Methods: We convened 61 highly-productive specialists and contacted 8 tES companies to assess 71 issues related to tES digitalization readiness, and processes, barriers, advantages, and opportunities for implementing tES digital trials. Delphi-based recommendations (>60% agreement) were provided.

Results: The main strengths/opportunities of tES were: (i) non-pharmacological nature (92% of agreement), safety of these techniques (80%), affordability (88%), and potential scalability (78%). As for weak- nesses/threats, we listed insufficient supervision (76%) and unclear regulatory status (69%). Many issues related to methodological biases did not reach consensus. Device appraisal showed moderate digitalization readiness, with high safety and potential for trial implementation, but low connectivity.

Conclusions: Panelists recognized the potential of tES for scalability, generalizability, and leverage of digital trials processes; with no consensus about aspects regarding methodological biases.

Significance: We further propose and discuss a conceptual framework for exploiting shared aspects between mobile-Health tES technologies with digital trials methodology to drive future efforts for digitizing tES trials.

Graphical Abstract. tES Digital Trial Consensus Roadmap
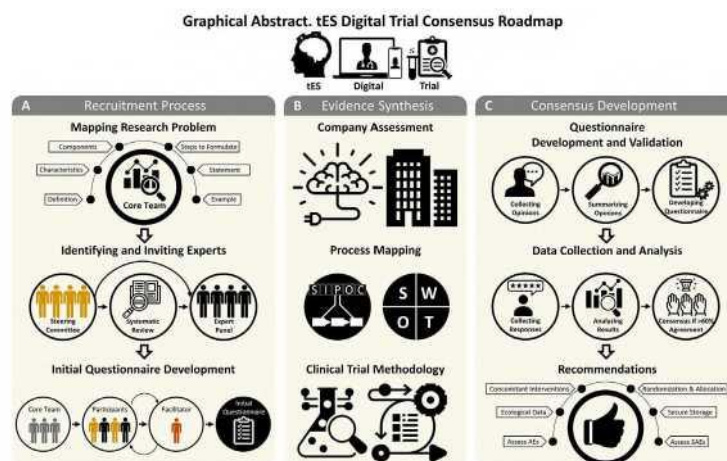
1. Introduction

Transcranial electric stimulation (tES) is a non-invasive neuromodulation intervention that uses electric currents applied over the scalp to modify cortical activity and treat neuropsychiatrie disorders and has high safety and tolerability (Fregni et al., 2021). Notwithstanding, due to its low-to-moderate efficacy for several conditions, the consensus of its readiness for clinical use across indications varies (Ekhtiari et al., 2019; Fregni et al., 2021), and regulatory approvals across regions are mixed (Bikson et al., 2018b; Fregni et al., 2015), warranting larger-scale clinical trials (Brunoni et al., 2012). However, these trials are hampered by the need for daily visits to the research center to deliver the necessary number of tES sessions, limiting recruitment, harming adherence, increasing costs (Brunoni et al., 2012), and restricting diversity (Bikson et al., 2018a; Charvet et al., 2020).

Unlike other non-invasive neuromodulation modalities, tES devices, by virtue of being low-intensity and battery-powered, can be designed to be portable, (Woods et al., 2016) intervening an appealing brain stimulation modality for patients who do not tolerate pharmacotherapy (Brunoni et al., 2019) or have difficulty attending treatment at a clinical center. Over the past few years several companies have been designing highly-deployable tES devices that could be used to address issues of scale, access, and patients' burden in the context of digital trials - i.e., trials that leverage aspects such as recruitment, assessment, and data analyses through the implementation of digital technologies (Inan et al., 2020). These approaches could be further integrated with mobile Health devices, apps, and wearables, allowing for several new implementations, such as simultaneous combination with cognitive and psychological interventions, ecological momentary assessment of behaviors, passive data collection, and digital phenotyping (Insel, 2018; Torous et al., 2017).

However, since protocols and standards for digital trials using mobile tES are still emerging, the challenges and opportunities of their implementation processes have not yet been systematically examined. Moreover, issues on rigor and reproducibility - for instance, best practices to perform randomization, allocation concealment, and sham stimulation - and generalizability - how to fully explore their potential for scalability while ensuring adherence and representativeness - have only been discussed in nondigital contexts (Bikson et al., 2018a; Charvet et al., 2020, 2015). Finally, implementation challenges are different in low-/middle- income countries, which present lower digital literacy, fluency in non-native languages, and wireless connectivity (Silva-Filho et al., 2022); conversely, scalable mobile Health interventions have even higher impact potential in such countries (Torous et al., 2021).

Considering these challenges, we systematically identified non- invasive neuromodulation specialists to elaborate and discuss issues related to the extent, processes, and methodological characteristics of digitizing non-invasive neuromodulation trials. These findings, supplemented by a systematic scoping review of tES clinical research articles and an assessment of the digitalization degree of commercially available tES devices, provided a key summary of Delphi-based recommendations for enhancing the implementation of digital tES trials. Therefore, the aims of this consensus statement are to (1) identify commercial tES devices available and their characteristics suitable for remote use, (2) discuss the implementation of tES digital trials by performing a

systematic scoping review and strategic process mapping, and (3) evaluate methodological aspects of tES digital trial designs. Based on these aims, we present (1) a key summary of Delphi-based recommendations for implementing digital trials using tES, and (2) methodological aspects that warrant further investigation according to this new approach.

2. Methods

Our protocol was pre-registered at the Medrxiv (Brunoni et al., 2022) and is depicted in Fig. 1. Minor deviations occurred (Supplementary Material - Appendix 1).

2.1. SPECIALIST PANEL

We used a Delphi technique, in which comments and feedback are iteratively discussed (Hsu and Sandford, 2007), for addressing challenges and proposing recommendations for digitizing tES trials. Following recent papers (Ekhtiari et al., 2022a, 2022b), we initially convened a steering committee (SC) group, formed based on the collaborative network of the leading authors, to develop structured questionnaires with items using Five-point Likert scales or open questions (Supplementary Material - Appendix 2). The SC also provided qualitative feedback on several topics that were analyzed by the leading authors and qualitatively described here. Afterward, the SC interacted with a larger expert panel (EP) to rate each item. The EP members were selected among the most productive authors in the field, identified through a systematic review of recent tES clinical trials in 10 years. AKZ, MZB, and PGA, searched and screened the PubMed database with the keywords regarding tES clinical trials from January 2011-December 2020. The title and abstract of the articles were screened independently and remaining conflicts were discussed with ARB and HE. Additionally, ARB reviewed each included study and performed an independent search using the same criteria. Authors' information were then extracted by the aforementioned group and sorted based on number of publications and authorship position (Supplementary Material - Appendix 3). Several interactions were performed between the EP and SC until a final manuscript version was assembled. The consensus was achieved by a >60% agreement of all panelists. Electronic questionnaires were used in all steps of this process.

2.2. SYSTEMATIC SCOPING REVIEW

A systematic scoping review (Levac et al., 2010) was performed to identify tES reviews, consensus papers, and guidelines to select characteristics for composing the questionnaires used in the rating phase (Supplementary Material - Appendix 4).

2.3. tES DIGITALIZATION READINESS

Companies producing tES devices were identified through specialist referrals and web search and surveyed using structured questionnaires to assess their digitalization readiness, according to connectivity, readiness for digital trials, parameter space flexibility, ecological footprint, front-end interface, and data security (Supplementary Material - Appendix 5).

2.4. PROCESS MAPPING AND METHODOLOGICAL ASSESSMENT

We used SWOT (Strengths, Weaknesses, Opportunities, and Threats) and SIPOC (Suppliers, Inputs, Process, Outputs, Customers) approaches to respectively identify external and internal negative and positive aspects for digitizing tES trials and map and compare processes related to standard and digital tES trials. The methodological assessment was based on perceived challenges and advantages, identified through questionnaires, of conducting such trials (Supplementary Material - Appendix 2).

2.5. ROLE OF THE FUNDING SOURCE

This work received no specific funding from any source.

3. Results

3.1. SPECIALIST PANEL

For the SC, 34 authors were invited and all agreed to participate. For the EP, out of 43 authors who were identified, 14 did not reply to our contacts, and 2 declined to participate (overall response rate: 79.2%). Finally, 27 participants constituted the EP (Supplementary Material - Appendix 6). Most panelists were men (70%), experienced (78% with >10 years of experience in the field), and between 40 to 49 years old (44% and 33% of the SC and the EP). They resided in the United States of America (USA) (SC n = 11, EP n = 3), Brazil (SC n = 6, EP n = 5), Germany (SC n = 5, EP n = 4), and 13 other countries (Supplementary Material - Appendix 7). Only 15% and 18% of the SC and EP members, respectively, were not conducting at least one tES trial with digital features; most were principal investigators (83%) of such trials.

3.2. SYSTEMATIC SCOPING REVIEW

Our initial search yielded 443 references, and 34 articles met the inclusion criteria of our scoping review, including 9 recommendation articles (Bikson et al., 2018a; Deer et al., 2014; Fregni et al., 2015; Fried et al., 2021; Kim et al., 2020; Sandars et al., 2016; Sierawska et al., 2019; Thibaut et al., 2017; Zhang et al., 2019), 10 guidelines (Antal et al., 2017; Bikson et al., 2020; Charvet et al., 2020, 2015; Cruccu et al., 2016; Fregni et al., 2021; Gillick et al., 2018; Lefaucheur et al., 2017; Legatt et al., 2016; Parikh et al., 2016), 10 critical reviews (ALHarbi et al., 2017; Cappon et al., 2016; Godeiro et al.,

2021; Lucchiari et al., 2018; Maatoug et al., 2021; McClintock et al., 2019; Sanches et al., 2021; Santos et al., 2021; Shiozawa et al., 2017; Workman et al., 2020), and 5 expert consensus articles (Baptista et al., 2019; Buch et al., 2017: Ekhtiari et al., 2019; Grimaldi et al., 2014; Martelletti et al., 2013), which were used for elaborating the study questionnaires (Supplementary Material - Appendix 8).
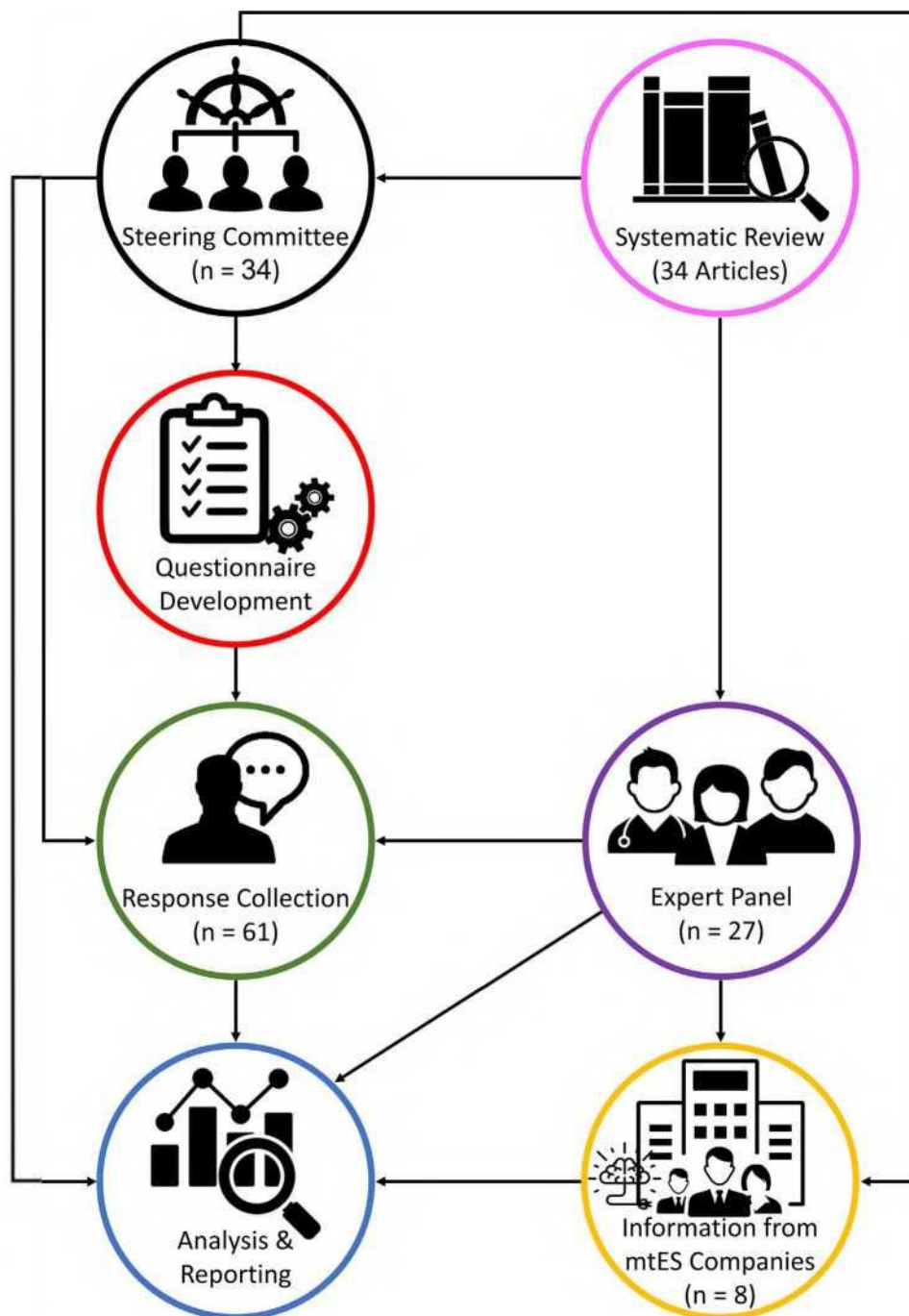

Figure 1. Study workflow. First, the steering committee (SC) was formed, including prominent researchers in the field. Then, supplemented by the results of a systematic review conducted on transcranial electric stimulation (tES) trials, the SC developed the questionnaire, which was sent to all participants of the study (SC and expert panel (EP)) to answer it.

Simultaneously, companies producing tES devices were contacted, based on the companies known by the SC and EP, to provide details about the available devices. Finally, the SC analyzed the data received from the questionnaire and all participants took part in reporting the results.

3.3. tES DIGITALIZATION READINESS

Eight of 13 companies contacted provided feedback. Digitization readiness varied according to their wireless connectivity, readiness for digital trials, the flexibility of parameter space, ecological footprint, front-end interface, and data security. Markedly, current systems have limited wireless connectivity, which is a barrier for device-to-device communication with wearables and third- party apps that could enhance portability potential (e.g., apps collecting biological data, and mobile mental health apps). Conversely, most systems currently present good data security protocols (reported Health Insurance Portability and Accountability Act [HIPAA] or General Data Protection Regulation [GDPR] compliance), the flexibility of tES parameter space, and readiness for digital trials (Fig, 2).
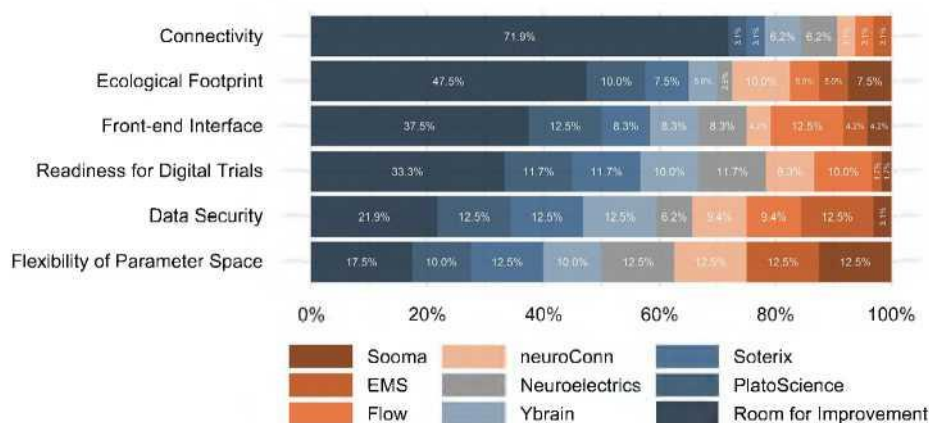

Figure 2. Digitalization readiness of tES devices. Based on the feedback of 8 out of 13 major transcranial electric current stimulation (tES) companies, we evaluated the readiness of these systems for digital trials, considering their connectivity (capability of communicating with other devices and the Web, due to the presence of Bluetooth, Wi-Fi, 3G⁄4G⁄ 5G, and communication with third-party apps), methodological aspects (randomization, sham, blinding, built-in data collection, optional data collection, and optional research dashboard), parameter space flexibility (current intensity, session duration, number of sessions, electrode positioning), ecological footprint (rechargeability and replaceability of batteries, recyclability and reusability of sponges, and recyclability of devices), front-end interface (smartphone app, touch screen, device itself, no interaction), and data security (compliance to laws such as GDPR, mention of encryption and anonymization procedures, and option for not collecting sensitive data). The questionnaires and rating systems are described in the Supplementary Material - Appendix 5.

3.4. SWOT ASSESSMENT

The identified characteristics and quantitative agreement rating composing the SWOT assessment are displayed in Fig. 3. Qualita- tive aspects are briefly discussed here and detailed in the Supplementary Material - Appendix 9.

Regarding strengths, the panelists agreed on four features: (a) high safety, considering previous evidence from non-digital trials and studies in humans (Antal et al., 2017; Aparício et al., 2016; Bikson et al., 2016; Moffa et al., 2017); (b) feasibility of selfapplication, owing to recent developments of

devices in which electrode placement is fixed, methods for easy strap positioning, and friendly end-user interface of mobile tES device (Charvet et al., 2020); (c) being a non-pharmacological intervention; and (d) affordability, as tES devices are simple to be built in terms of electric engineering (Woods et al., 2016), costs of high-end features (e.g., microprocessors, Bluetooth and wireless connectivity, miniaturization) are decreasing over time, and self-application saves human resources (Supplementary Table 6).

Regarding weaknesses, panelists agreed on two aspects: (a) difficulties in remote supervision, raising concerns regarding patients themselves manipulating tES devices, which could lead to misuse, diversion of the device, or its use outside of medical contexts, further impacting on the reproducibility of findings; (b) and difficulties in obtaining accurate placement of electrodes, as deviations in electrode positioning and orientation might affect outcomes (Woods et al., 2016). Therefore, companies should develop and test new methods for assuring the correct placement of electrodes (Fried et al., 2021). Other potential weaknesses did not reach consensus, such as concerns related to bioethics, particularly regarding equity to access; increased (compared to on-site tES trials) risks of common and serious adverse events (Lefaucheur et al., 2017); and relatively low evidence of clinical efficacy for most conditions (Fregni et al., 2021) (Supplementary Table 7).

Regarding opportunities, six aspects reached agreement: (a) scalability, as, compared to on-site tES trials that need physical space, staff to apply sessions and commute of participants, digital trials using mobile tES devices do not have such constraints, allowing research assistants to monitor several participants at once, at any distance from the study centers; (b) telemedicine, which has been widely adopted during the COVID-19 pandemic, facilitating its adoption in digital trials; (c) employment of combined mobile Health technologies, permitting digital phenotyping (Torous et al., 2017) and combination with digital interventions when using paired wearables and smartphone applications; (d) automatization of procedures (see SIPOC below); (e) 5G/Internet of Things, which can boost connectivity and data processing, leveraging data collection (Torous et al., 2017) and eventually allowing the development of mobile closed-loop tES systems (Sanches et al., 2021); and (f) use of design thinking approaches, i.e., customizing mobile tES devices around the patients perspectives (Polhemus et al., 2020), for instance, to accommodate those with physical or cognitive impairments (Supplementary Table 6).

Finally, two threats reached a consensus: (a) recreation and do- it-yourself misuse, which could lead to unexpected adverse events and safety issues (Sierawska et al., 2019); and (b) regulatory status, as medical devices require formal regulatory approval in the USA (Darrow et al., 2021) and Europe (Antich-Isern et al., 2021), although some tES devices are marketed as wellness devices, have regulatory device exemptions (Bikson et al., 2018b), or can be approved by similarity (Bikson et al., 2018b). Further, mobile tES devices could have additional regulations, if framed as mobile Health systems (Onodera and Sengoku, 2018). Additionally, two potential threats were identified by most of the panel, but did not reach the 60% consensus threshold: (a) risks related to hacking and cyber-security, as observed in mobile Health devices (Aljedaani and Babar, 2021), and (b) risks related to confidentiality and anonymity (Supplementary Table 7).

3.5.   SIPOC

We identified four main processes (recruitment, pre-screening, screening, and participation) in which digitization and automatization procedures can leverage mobile tES trials (Table 1). The panelists noted that trials might not be purely digital or analog, and different degrees of digital features can occur at each process. For instance, participants can be recruited through social media but screened onsite. Moreover, digital processes can provide enhanced metrics to adjust processes, recruit faster, and follow participants for longer periods. Finally, digitization processes provide scalability due to the use of digital assessments and telemedicine (Table 1).

Table 1
Comparison of SIPOC processes of trials in which digital features are present and absent.

Digital features	Suppliers	Inputs	Outputs	Clients
Process: Recruitment				
Absent	Traditional Media	Telephone call or email	Pool of volunteers constrained due to geographical barriers	Pre-screening/ screening onsite teams
Present	Targeted Social Media and Google Ads, public segmentation	Electronic forms, ChatBots	Larger pool of volunteers	Online pre-screening/ screening teams
Process: Pre-screening				
Absent	Volunteers	Onsite checklist of eligibility criteria	Potential Participants	Onsite screening team
Present	Volunteers	Online assessments, AI techniques can increase the likelihood of inclusion	Potential Participants	Online screening team
Process: Screening				
Absent	Potential participants	Onsite clinical interview; written consent	Participants	Onsite clinical team
Present	Potential participants	Clinical interviews aided by digital assessments; digital consent	Participants	Online clinical team
Process: Participation in the trial				
Absent	Participants	Staff delivers tES sessions and assessments	Completers and patients who dropped out	Trial complete; possibly follow-up studies
Present	Participants	tES devices shipped to participants; online videos and telesupport to guide self-applied tES; digital assessments via online interviews and mHealth technologies	Completers and patients who dropped out	Trial complete; possibly follow-up studies

The table illustrates how processes of clinical trials can be leveraged using digital approaches. In (a) recruitment, volunteers, unconstrained by geographical barriers, can fill out electronic forms and be automatically excluded according to eligibility criteria; (b) pre-screening, potential participants can be scheduled and contacted automatically for online screening (a step that can be enriched by using machine learning algorithms); (c) screening, enrolled participants can provide digital consent, have transcranial electric stimulation (tES) devices shipped to their homes, and being instructed how to use them via videos and/or augmented reality techniques; and (d) participation in the trial, interaction with the staff can be mediated by psychiatric chatbots for filtering between simple questions, reporting of adverse events and need of medical care.

3.6.   METHODOLOGICAL ASPECTS

The panelists examined 24 methodological aspects of digital trials using mobile tES devices, reaching consensus in 12 of them (Fig. 4). They are briefly discussed here and detailed in the Supplementary Material - Appendix 10.

Of the 12 aspects that reached consensus, 10 were perceived as advantages of digital trials, which included (a) the adoption of different study designs, including (b) adaptive designs, as adaptation rules can be performed automatically and remotely whether data are collected and analyzed by mobile tES systems. Panelists also considered that (c) tES devices are already sufficiently developed to be used remotely, which allows for (d) longer follow-up periods and (e) higher recruitment rates, being (f) faster and more efficient than on-site trials. Also, (g) greater external validity compared to on-site trials were perceived. Finally, other advantages were the potential for (h) collecting more data than on-site trials, (i) combination with other therapies and (j) scalability. The 2 disadvantages/challenges that reached consensus were: (a) the necessity of validating new tES parameters, methodologies, and indications first in on-site studies, and (b) the need of developing better remote

assessment methods, such as behavioral clinical scales properly designed and validated to be employed remotely (Supplementary Table 8).

The items that did not reach consensus mostly pertain to internal validity issues. Interestingly, a significant portion of panelists was undecided on these issues (Fig. 5). Of note, interesting remarks (detailed in Supplementary Material - Appendix 10) were made for: (a) randomization-allocation procedures that are done using either specific devices or apps/software, but can be vulnerable to contamination biases due to hacking and exposure of the randomization list; (b) study blinding, as blinding breaking can occur if devices are manipulated; (c) sham stimulation, which can also be revealed due to device manipulation.
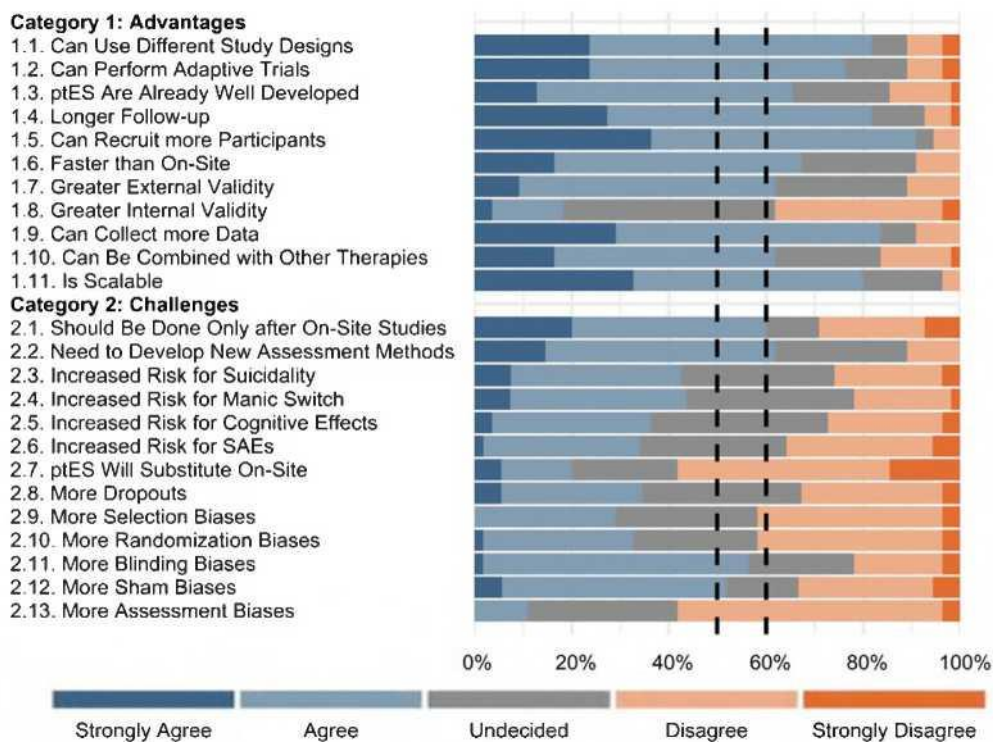

Figure 4. Ratings for advantages and challenges of conducting tES digital trials. This figure depicts the ratings of 55 61 raters (24 34 from the steering committee and 31 27 from the expert panel) for methodological aspects of tES. Each item was rated from strongly disagree to strongly agree. In ratings for the advantages of transcranial electric stimulation (tES) digital trials from a methodological perspective, only one item (1.8. Greater internal validity) did not reach the agreement threshold of 50% (rated as either agree or strongly agree by more than 50% of the respondents). All of the other items in this category also reached a more stringent threshold of 60%. However, in ratings for challenges of tES digital trials from a methodological perspective, 9 items (2.3. Increased risk for suicidality, 2.4. Increased risk for the manic switch, 2.5. Increased risk for cognitive effects, 2.6. Increased risk for SAEs, 2.7. ptES will substitute on-site, 2.8. More dropouts, 2.9. More selection biases, 2.10. More randomization biases, and 2.13. More assessment biases) did not reach the 50% threshold of agreement. With a more stringent threshold of 60%, two additional items (2.11. More blinding biases and 2.12. More sham biases) dropped out from the agreement. Items are represented by their summary in the figure. Full texts of the items are provided in Supplementary Table 3. ptES = portable transcranial electrical stimulation. SAE = serious adverse event.
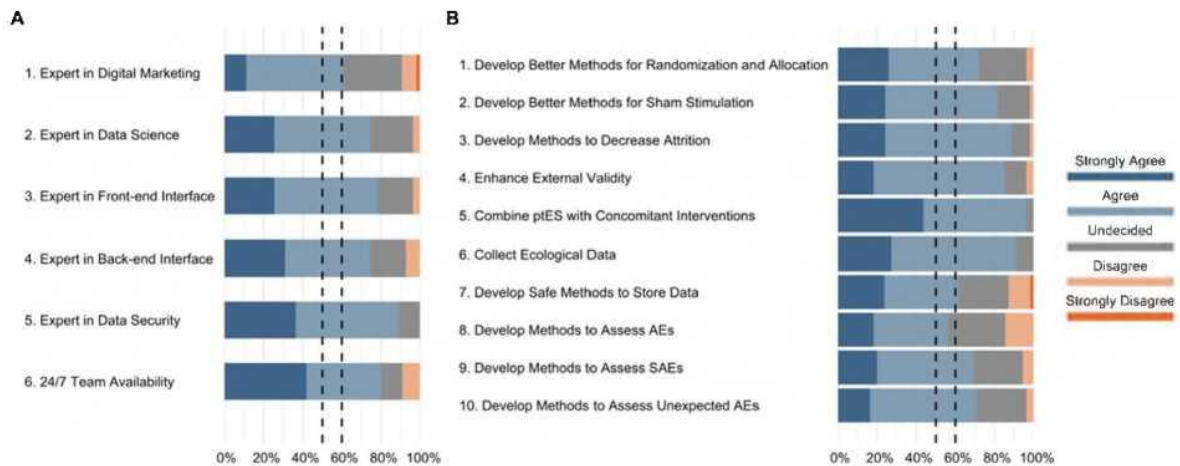
Figure 5. Ratings of the tES clinical trials team features and general recommendations on digitizing tES trials. This figure depicts the ratings of 55 61 participants (24 34 from the steering committee and 31 27 from the expert panel) for the ptES clinical trials team features (A) and general recommendations for digitizing ptES clinical trials (B). Each item was rated from strongly disagree to strongly agree. In ratings for the ptES clinical trials team features (A), all of the items have reached the 50% threshold of agreement (rated as either agree or strongly agree by more than 50% of the respondents). These items have also reached a more stringent threshold of 60%. Similarly, in ratings for the general recommendations for digitizing ptES clinical trials (B), all of the items have reached the 50% threshold of agreement. However, with a more stringent threshold of 60%, one item (8. Develop methods to assess AEs) dropped out from the agreement. Items are represented by their summary in the figure. Full text of the items is provided in Supplementary Tables 4 and 5. ptES = portable transcranial electrical stimulation. AE = adverse event. SAE = serious adverse event.

3.7. RECOMMENDATIONS

The panelists recommended that teams performing tES digital trials should have members specialized in (a) digital marketing strategies, to enhance online recruitment; (b) data science and visualization, for data collection and analysis; (c) front-end interfaces, to enhance user experience; (d) back-end programming; (e) issues related to data security, integrity, anonymity, and replicability. Also, they suggested that (f) a team member should be always ("24/7") available (Fig. 5) (Supplementary Table 9).

Regarding further research, most panelists recommended that better methods for (a) randomization/allocation, and (b) sham should be explored. Also, further research was recommended to develop or refine methods to enhance (c) adherence and (d) external validity of the trials. Also, more research should be devoted to aspects such as (e) combination of interventions, (f) biobehavioral data collection, (g) enhanced data security, and methods to assess (h) serious and (i) unexpected adverse events (details in Supplementary Material - Appendix 11, Supplementary Table 10).

4. Discussion

By convening a diverse group of 61 worldwide specialists in the field of non-invasive neuromodulation, we performed the first systematic assessment and Delphi-based validation of

perceived challenges, opportunities, methodological issues, and recommendations on digitizing non-invasive neuromodulation trials. We used several strategies to organize and describe these assessments, such as processing mapping strategies, a systematic scoping review of the literature, iterative rating and validation of structured questionnaires by specialists, and assessment of the digital readiness of commercial tES devices. Taken together, our findings show that performing digital trials using mobile tES devices has complementary advantages and can overcome major on-site tES trial challenges, namely the intensive treatment schedules (Thibaut et al., 2017), transportation costs, accessibility, and scalability (Charvet et al., 2020). By performing trials remotely, dislocation burdens are decreased, as well as the need for space at the research center, and of trained staff for delivering tES sessions, aspects that increase the trial duration (Brunoni et al., 2012; Parikh et al., 2016, p 4). Additionally, tES devices are highly sealable, as a single team member can monitor several people at once, provided that tES devices are easy to manipulate, handle, and can be self-delivered. Such scalability gains could be leveraged in faster trials with larger sample sizes, longer follow-up periods, and employing digital recruitment strategies. Considering our results, we propose and further discuss a conceptual framework for digitizing neuromodulation, combining concepts of digital clinical trials with mobile tES (Fig. 6).
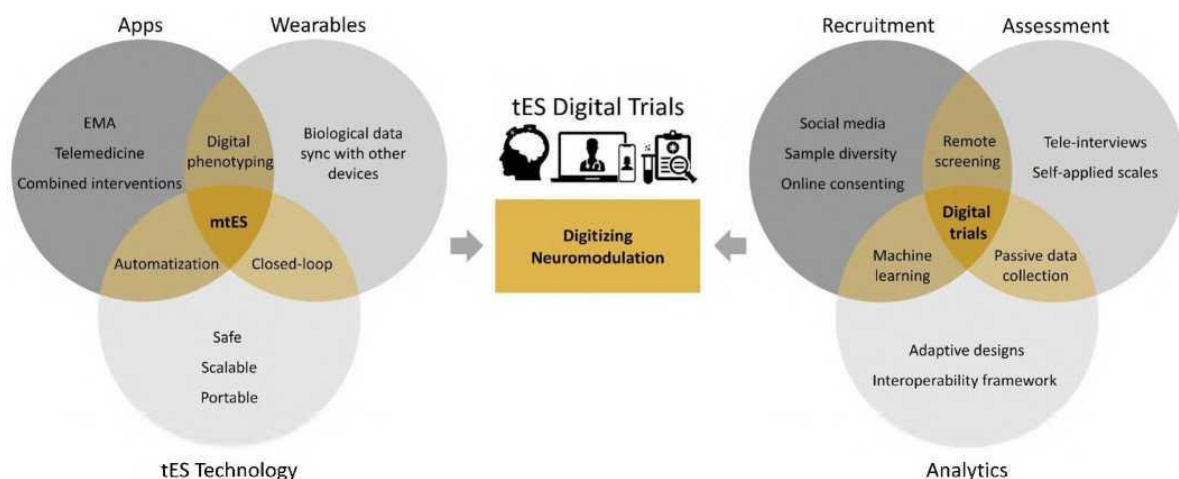

Figure 6. A conceptual framework for digitizing neuromodulation. As depicted on the left side of the figure, transcranial electric stimulation devices had been relatively simple, essentially using batteries connected to electrodes to deliver constant currents, and contain few (micro) electronic components. Although portable and safe, they had not been specifically designed for use outside hospital or academic center settings. New and future generations of tES will be mobile Health tES systems using digital technologies for improving health outcomes. They are and will be smaller and lighter than previous generations, possessing wireless connectivity. Such devices are already used at home and are self-delivered, usually with some degree of remote supervision. Their use will be supported by proprietary or third-party apps and wearables. Resulting together with the aforementioned concept as digitizing neuromodulation, the right side of the figure shows digital trials as clinical trials that use digital features to enhance recruitment, assessment, and data analysis and could unleash the full potential of tES regarding scalability and equity of access. There are many similarities between the assumptions of digital trials and the capabilities of mtES, which are discussed in this work. EMA = Ecological momentary assessment. mtES = mobile transcranial electrical stimulation.

4.1. MOBILE tES DEVICES

To the best of our knowledge, the term "mobile tES" has not been used yet to describe the combination of highly-deployable neuromodulation devices paired with other wearables or apps. This terminology frames tES in the context of mobile Health devices (Onodera and Sengoku, 2018), encouraging the exploitation of contact points between these two growing fields. However, even though several issues for deployable and remote use have already been addressed (e.g., decreasing prices, rechargeable batteries, tailored sponges, sham stimulation, easiness of electrode positioning, and programming session stimulation parameters), our findings showed that no commercial tES devices have been fully digitized yet, presenting different degrees of online, wired, or wireless connectivity. Also, especially for offline devices, methods for restricting the number of sessions allowed per day were not identified. Additionally, most systems neither collect active or passive data, nor present friendly-user interfaces.

The panelists agreed on several opportunities; however, most are distant from immediate implementation. For instance, device-to-device communication ("Internet of Things") would need pairing with third-party apps or wearables, which is not yet available. This limits other perceived opportunities such as digital phenotyping, combination with psychological or cognitive app interventions, and seamless automatization with other platforms and digital processes.

4.2. METHODOLOGICAL CHALLENGES, ADVANTAGES, AND PROCESSES OF DIGITAL TRIALS

The impact of digitizing neuromodulation trials on external validity seems mostly positive, considering that subjects who would not be enrolled in on-site trials are reached. On-site trial samples are likely to be composed of those with free time and/or living near the clinical center to receive the sessions. Notwithstanding, it is still possible that those younger, richer, more educated, with higher digital literacy, and living in urban areas are preferentially enrolled in digital trials. Also, if recruitment strategies are performed solely using social media, the trial results would have restricted generalizability for people that do not use such media. This could be overcome by using segmented digital marketing campaigns. Likewise, attrition rates might not necessarily be lower in digital trials - although not needing to return daily to the clinical center could decrease the burden and minimize dropouts, samples from digital trials might face less engagement and more difficulties in self-delivering the sessions. The lack of daily contact with the clinical staff could also decrease motivation and increase dropouts. In addition, direct social contact, social support, and social connectedness outside the digital environment can influence attrition rates of clinical trials. Therefore, telemonitoring and proper interaction with participants, managing their expectations and credibility of the team, and reinforcing the need to abide by the study protocol, could avoid dropouts.

Panelists also emphasized that methodological issues that have not been completely addressed in on-site trials can be magnified in digital trials (Charvet et al., 2015; Fried et al., 2021). For instance, if the process of randomization - allocation concealment - is hacked from the server and publicly

exposed, the entire trial can be lost (or, at least, suspended until a new list is generated). Moreover, blinding and sham stimulation issues are not completely resolved issues in on-site trials (Fonteneau et al., 2019), and biases arising from these steps are more likely to occur (e.g., sham stimulation can be unconcealed by measuring the voltage between electrodes (Woods et al., 2016)) and harm the entire study (for example, by exposing methodological vulnerabilities on the Web). Additionally, issues that would be minor in on-site trials might be more relevant in online trials. For instance, stimulation sessions can be performed in on-site trials appropriately and guarantee adherence (Woods et al., 2016), but, in digital trials, some degree of remote monitoring would be necessary for ensuring these aspects.

Finally, there are unique new challenges for digitizing neuromodulation. Even though cyber-hacking is not usually discussed in the environment of clinical trials, government and big company systems are being increasingly hacked. Data anonymity and confidentiality are additional aspects of vulnerability more relevant than in on-site trials, if, for instance, information is also recorded in the devices, smartphones, or is transmitted remotely. Data collection using standard behavioral scales (for instance, scales for depression) and adverse events need to be further validated to be used online and remotely to avoid instrumental biases. Finally, even open pre-publication of study protocols, which enhances transparency and reproducibility, cannot be fully detailed in digital trials, as a complete description of the groups, blinding methods, and sham stimulation of the protocols could be harmful to the internal validity of digital trials (Charvet et al., 2020, 2015).

4.3. LIMITATIONS

Although we systematically reviewed the literature for selecting the most productive authors in neuromodulation, experts publishing in non-English databases might not have been selected. In addition, most of the panelists are from high-income countries, limiting the experience, feedback, and the number of votes of panelists from low-/middle- income countries, where 85% of the world population lives, and with probably additional issues on digitalization, including availability. Similarly, there is predominance of English-speaking countries, with lack of participation of Asian countries/regions such as China, Japan, Korea, and Taiwan. Future studies must increase the representativeness of other regions to increase the external validity of our recommendations. Moreover, our search might not have identified emerging young experts as we have established a threshold based on the number of publications. Although we considered different methods for composing the EP, such as "snowball sampling" based on recommendations from the SC members, and search of other databases such as clin- icaltrials.gov, preprints, and conference publications, these pro-cesses would be non-systematic or involve gray areas in the literature. We also did not assess other stakeholders besides people from industry and academia that could have been relevant for our work, such as patients, governmental and non-governmental organizations. Moreover, only 8 of 13 companies replied to our contacts, despite several emails that were sent to reach them, and even offering the possibility of online meetings to discuss this work. Although we could have extracted company information based on public information, we opted not to do that as some information could have been inaccurate. Moreover, our study is limited in number of rounds

compared to other Delphi panels' studies, which may have influenced the final overall results. Finally, no large tES digital trials have been finished and published yet; therefore, the processes and challenges described here are mostly theoretical and should be iteratively updated as the field develops. Interestingly, the lack of consensus on issues related to its disadvantages, risks, and biases, with many specialists remaining undecided, indicates that the field is still in its infancy.

4.4. FUTURE DIRECTIONS

The recommendations for teams conducting digital neuromodulation trials markedly diverge from on-site trials that are centered on clinical specialists and staff trained in performing biomedical procedures. The feasibility of these recommendations should be further debated, as they would require more resources. Most recommendations fit with companies and for pivotal studies, and not necessarily for teams running pilot studies that would not have all the capabilities recommended above. For instance, third-party services could be contracted to do specific tasks related to software and hardware development, or such aspects could be developed together by researchers and companies. Moreover, recommendations such as a support team being always available for medical urgencies, although optimal, might be unrealistic even with large resources. Such issues would need to be carefully discussed with internal review boards and ethics committees to guarantee patient safety without harming trial feasibility. The recommendations for further research in some aspects specifically related to internal validity, and also external validity, were largely convergent, reaching 70—80% agreement rates. Taken together, these recommendations call for new standards and best practices of fundamental pillars of tES clinical research, such as methods for sham stimulation, randomization, allocation, and assessment of adverse events. These methodologies have been steadily built over the last decade (Bikson et al., 2018a; Brunoni et al., 2019, 2012) and, although challenged in certain aspects such as sham and blinding (Fonteneau et al., 2019; Turner et al., 2021), they have been largely used in clinical trials (Fried et al., 2021). Although several approaches could be used, in a first step relatively simple randomized studies involving healthy participants could use parameters such as blinding efficacy and rate of adverse events as outcome measures, comparing whether they are different in those receiving on-site vs online tES. Pilot studies using mobile tES in clinical samples are also encouraged to report their methodological approaches and challenges (Alonzo et al., 2019; Eilam-Stock et al., 2021). Furthermore, the implications of using home-based stimulation regarding cost optimization and insurance coverage are essential for the field development. Future cost-benefit and implementation studies are needed to proper assess these topics. Finally, it is worth to mention that the division between digital trials and classic on-site studies is mainly illustrative; in reality, on-site trials will progressively implement digital features, so there is a continuum between on-site and on-line studies. These new approaches can be used to validate the efficacy of new tES stimulation protocols (pivotal phase III trials) and test their real-world effectiveness (pragmatic trials and cohorts).

5.   Conclusion

In this first Delphi Panel evaluating opportunities, risks, and methodological issues regarding digitizing tES trials, we provided a landscape of this new approach and reached a consensus on several recommendations that should be evaluated in further studies. The panel of specialists agreed on the advantages associated with the implementation of tES trials; however, considering the fastgrowing digitalization in Medicine and Biotechnology, there is a pressing need to better understand how to adapt tES trials to be performed remotely, with a clearer knowledge regarding its positive and negative aspects.

Appendix A. Supplementary material

Supplementary data to this article can be found online at
https://doi.org/10.1016/j.clinph.2022.08.018

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