Brain Stimulation 16 (2023) 564–566

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

European reclassification of non-invasive brain stimulation as class III medical devices: A call to action

Within the European Union (EU), and by contrast with other countries (notably the USA), only a limited number of insurance companies reimburse treatment with repetitive transcranial magnetic stimulation (rTMS) and none with transcranial electrical stimulation (tES). As a consequence, there is significant risk that treatment availability and investment in research and clinical developments in non-invasive brain stimulation (NIBS) in Europe will fall behind. Unexpectedly, a sudden unwelcome regulatory change has made the European situation even worse. In December 2022 the EU reclassified rTMS and low intensity tES as Class III devices, the category of highest risk (https://eur-lex.europa.eu/eli/reg_impl/2022/2347/oj). Under the previous regulatory framework (Medical Devices Directive, MDD), the EU did not specifically regulate NIBS devices, but most were classified as Class IIa (manageable risks, approved treatment effects). Class III devices, such as deep-brain stimulation implants, are defined as invasive, because they connect directly to the circulatory or central nervous system. Although this new reclassification currently refers only to "*products without an intended medical purpose*", (a terminology that is for many researchers and medical doctors unclear) - the evidence adduced about the risks and adverse effects of rTMS and tES - which serves as the justification for this reclassification - is gravely flawed. The EU has apparently assessed that NIBS poses a greater risk to patients' safety than previously thought. This assessment is based on incorrect statements about rTMS and low intensity tES that contradict the available scientific evidence, and many of the stated claims and assumptions are simply false (*e.g.* it is claimed that TMS/tES can induce "atypical brain development" or "abnormal patterns of brain activity"). Likewise, the prominent mentioning of rTMS/tES-related seizure risks contradicts the most recent consensus statement in the field based on actual clinical data, which demonstrated that observed seizure rates are so much lower than previous guidelines advised. The prior caution about seizure risk is no longer supported by scientific evidence [1,2].

How this EU ruling was established is hard to understand. Apparently, in May 2021, a new Medical Device Regulation (MDR) was introduced, and NIBS was specifically addressed for non-medical use in Annex XVI. The application of MDR will be gradual, through a 'transition period' (Article 120) until May 2024, meaning that existing NIBS products (of Class I and Class IIa from the previous MDD), are allowed to stay on the market until the end of this period, as long as they comply with the transition rules.

In July 2022 "*certain EU Member States jointly requested the reclassification of several active products without an intended medical purpose*" (Annex XVI), including NIBS devices. The reasons why this request was made is not clear. In a very quick process an EU group called SANTE (Directorate-general for Health and Food Safety) prepared a draft and this draft was published for an 8-week hearing period on the *Have Your Say* platform. To the best of our knowledge, no experts in the field or NIBS companies were notified about this. The draft received only 22 comments from the public and almost all of them were related to non-NIBS devices. On December 1st, 2022 the final version of the reclassification was published and it became effective in law from 22nd December. Now all new non-medical NIBS products in the EU have to comply with Class III rules.

The European Society for Brain Stimulation (ESBS), founded in 2022, is an independent professional association of medical doctors, psychologists, neuroscientists, and others who specialize in research and clinical application of NIBS techniques. The mission of the ESBS is to represent and promote the field of NIBS research and clinical practice in Europe based on the latest scientific evidence.

The ESBS strongly opposes this EU ruling, which will have significant negative consequences for the future of our field.

Safety is our first priority. Over the past 30 years data has been collected by our field to carefully assess the behavioral, neurocognitive, physiological, and biophysical effects of NIBS on the central nervous system. These studies have not only informed us about clinical efficacy, but have also yielded new evidence-based non-pharmacological NIBS treatments for neurological and psychiatric disorders that are used in a growing number of countries worldwide. Importantly, this long research period has also informed us about the risks, adverse and side effects that can occur when applying NIBS. Based on this vast amount of safety data collected, several publications, meta-analyses, reviews, guidelines and consensus papers have provided peer-reviewed evidence-based assessments of the safety of rTMS (*e.g.*, Refs. [1–5]) as well as tES (*e.g.*, Refs. [5–8]), including in children [9]. *The current scientific and clinical evidence suggests both rTMS and low intensity tES are safe treatment and research interventions with few and mild adverse effects.*

As the ESBS, we agree that all NIBS devices must be certified as medical devices, class IIa, which indicates moderate risk, and used for diagnosis, monitoring and/or treatment.

However, we disagree with the Class III designation. To reclassify NIBS devices as having the same level of risk *as invasive brain*

https://doi.org/10.1016/j.brs.2023.02.012

stimulation devices that are implanted inside the brain, is inappropriate, contradicts 30 years of safety data, and has been decided without consultation of relevant professional stakeholders. In the short term, this reclassification will result in higher costs and substantial delays in NIBS research and development, undermining the world-leading role of European researchers in the field of NIBS. In the medium term, this EU decision will ultimately make NIBS treatment less accessible to patients in Europe and it will seriously hamper research, device development, and the search for new or more fine-tuned clinical indications. European citizens will be disadvantaged, and there is the risk that other treatment approaches with more serious and established adverse-effects will be over-used to compensate for the lack of NIBS availability. Consequently, we strongly protest this decision, and we urge our colleagues working in our field to do the same, regardless of nationality. We have already sent a protest letter to the EU. See also our website (MANIFESTO - brain-stimulation.eu website [10]) for more details https://www.brain-stimulation.eu/manifesto-eu-reclassification-of-nibs/eu-reclassification-action/.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J, Carpenter LL, Cincotta M, Chen R, Daskalakis JD, Di Lazzaro V, Fox MD, George MS, Gilbert D, Kimiskidis VK, Koch G, Ilmoniemi RJ, Lefaucheur JP, Leocani L, Lisanby SH, Miniussi C, Padberg F, Pascual-Leone A, Paulus W, Peterchev AV, Quartarone A, Rotenberg A, Rothwell J, Rossini PM, Santarnecchi E, Shafi MM, Siebner HR, Ugawa Y, Wassermann EM, Zangen A, Ziemann U, Hallett M. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. Clin Neurophysiol 2021;132(1):269–306. https://doi.org/10.1016/j.clinph.2020.10.003.

[2] Caulfield KA, Fleischmann HH, George MS, McTeague LM. A transdiagnostic review of safety, efficacy, and parameter space in accelerated transcranial magnetic stimulation. J Psychiatr Res 2022;152:384–96. https://doi.org/10.1016/j.jpsychires.2022.06.038.

[3] George MS, Taylor JJ, Short EB. The expanding evidence base for rTMS treatment of depression. Curr Opin Psychiatr 2013;26(1):13–8. https://doi.org/10.1097/YCO.0b013e32835ab46d.

[4] Perera T, George MS, Grammer G, Janicak PG, Pascual-Leone A, Wirecki TS. The clinical TMS society consensus review and treatment recommendations for TMS therapy for major depressive disorder. Brain Stimul 2016;9(3):336–46. https://doi.org/10.1016/j.brs.2016.03.010.

[5] Antal A, Luber B, Brem AK, Bikson M, Brunoni AR, Cohen Kadosh R, Dubljević V, Fecteau S, Ferreri F, Flöel A, Hallett M, Hamilton RH, Herrmann CS, Lavidor M, Loo C, Lustenberger C, Machado S, Miniussi C, Moliadze V, Nitsche MA, Rossi S, Rossini PM, Santarnecchi E, Seeck M, Thut G, Turi Z, Ugawa Y, Venkatasubramanian G, Wenderoth N, Wexler A, Ziemann U, Paulus W. Non-invasive brain stimulation and neuroenhancement. Clin Neurophysiol Pract 2022;7:146–65. https://doi.org/10.1016/j.cnp.2022.05.002.

[6] Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, Cohen LG, Dowthwaite G, Ellrich J, Flöel A, Fregni F, George MS, Hamilton R, Haueisen J, Herrmann CS, Hummel FC, Lefaucheur JP, Liebetanz D, Loo CK, McCaig CD, Miniussi C, Miranda PC, Moliadze V, Nitsche MA, Nowak R, Padberg F, Pascual-Leone A, Poppendieck W, Priori A, Rossi S, Rossini PM, Rothwell J, Rueger MA, Ruffini G, Schellhorn K, Siebner HR, Ugawa Y, Wexler A, Ziemann U, Hallett M, Paulus W. Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol 2017;128(9):1774–809. https://doi.org/10.1016/j.clinph.2017.06.001.

[7] Bikson M, Paneri B, Mourdoukoutas A, Esmaeilpour Z, Badran BW, Azzam R, Adair D, Datta A, Fang XH, Wingeier B, Chao D, Alonso-Alonso M, Lee K, Knotkova H, Woods AJ, Hagedorn D, Jeffery D, Giordano J, Tyler WJ. Limited output transcranial electrical stimulation (LOTES-2017): Engineering principles, regulatory statutes, and industry standards for wellness, over-the-counter, or prescription devices with low risk. Brain Stimul 2018;11(1):134–57. https://doi.org/10.1016/j.brs.2017.10.012.

[8] Bikson M, Brunoni AR, Charvet LE, Clark VP, Cohen LG, Deng ZD, Dmochowski J, Edwards DJ, Frohlich F, Kappenman ES, Lim KO, Loo C, Mantovani A, McMullen DP, Parra LC, Pearson M, Richardson JD, Rumsey JM, Sehatpour P, Sommers D, Unal G, Wassermann EM, Woods AJ, Lisanby SH. Rigor and reproducibility in research with transcranial electrical stimulation: an NIMH-sponsored workshop. Brain Stimul 2018;11(3):465–80. https://doi.org/10.1016/j.brs.2017.12.008.

[9] Zewdie E, Ciechanski P, Kuo HC, Giuffre A, Kahl C, King R, Cole L, Godfrey H, Seeger T, Swansburg R, Damji O, Rajapakse T, Hodge J, Nelson S, Selby B, Gan L, Jadavji Z, Larson JR, MacMaster F, Yang JF, Barlow K, Gorassini M, Brunton K, Kirton A. Safety and tolerability of transcranial magnetic and direct current stimulation in children: Prospective single center evidence from 3.5 million stimulations. Brain Stimul 2020;13(3):565–75. https://doi.org/10.1016/j.brs.2019.12.025.

[10] https://www.brain-stimulation.eu/manifesto-eu-reclassification-of-nibs/.

Chris Baeken
Faculty of Medicine and Health Sciences, Department of Head and Skin, Ghent Experimental Psychiatry (GHEP) lab, Ghent University, Ghent, Belgium

Department of Psychiatry, University Hospital (UZBrussel), Brussels, Belgium

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

Martijn Arns
Research Institute Brainclinics, Nijmegen, the Netherlands

Jerome Brunelin
CH Le Vinatier, Université Claude Bernard Lyon 1, CNRS, INSERM, Centre de Recherche en Neurosciences de Lyon CRNL U1028 UMR5292, PSYR2, F-69500, Bron, France

Lorena Chanes
Department of Clinical and Health Psychology-Institut de Neurociències, Universitat Autònoma de Barcelona, Catalunya, Spain

Serra Húnter Programme, Generalitat de Catalunya, Spain

Igor Filipcic
Psychiatric Hospital "Sveti Ivan", Zagreb, Croatia

Ana Ganho-Ávila
Faculty of Psychology and Educational Sciences, University of Coimbra, 3000-115, Coimbra, Portugal

Marco Hirnstein
Department of biological and medical psychology, University of Bergen, Bergen, Norway

Fady Rachid
Private Practice, 7, place de la Fusterie, 1204, Geneva, Switzerland

Alexander T. Sack
Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, the Netherlands

Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience (MHeNs), Brain+Nerve Centre, Maastricht University Medical Centre+ (MUMC+), the Netherlands

Jacinta O'shea
Oxford Centre for Human Brain Activity (OHBA), Wellcome Centre for Integrative Neuroimaging, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, OX3 9DU, UK

Giordano D'urso
Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples Federico II, Naples, Italy

Andrea Antal*
Department of Neurology, University Medical Center Göttingen, Germany

* Corresponding author.
E-mail address: aantal@gwdg.de (A. Antal).

31 January 2023
Available online 2 March 2023