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T4TE: Team for TMS–EEG to improve reproducibility through an open collaborative initiative

Dear Editor,

The use of combined transcranial magnetic stimulation (TMS) and electroencephalography (EEG) registration (TMS–EEG) in neuroscience research is currently facing a storm. While TMS–EEG has been considered a highly promising tool for probing human effective connectivity, the research field lacks consensus on the interpretation of signals and on several methodological issues, potentially leading to a replicability crisis. Here, we propose an international collaborative effort to collect large-scale datasets and to promote practice for robust data acquisition and analysis.

By measuring the neural activity produced by experimentally controlled and focal stimulation of the cortex, TMS–EEG has the potential to unveil neurophysiological mechanisms that can hardly be tested with other techniques. This is currently exploited in basic and clinical research with various aims and applications, including the exploration of core mechanisms such as oscillatory entrainment and effective connectivity, the development of biomarkers in neurological and psychiatric disorders and the development of a closed-loop system for optimization of TMS treatments [1].

Nevertheless, technical challenges and uncertainties still limit the use of TMS–EEG to a relatively small community of neuroscientists and hinder its clinical translation. Experts lack consensus on what is measured and what the good practices are to obtain genuine brain responses with minimal artifacts. Indeed, the artifactual contamination of some responses generated by TMS is still a debated controversy [2–4]. Moreover, there is no agreement on how to ensure high-quality data, to reduce artifacts during data acquisition and on how to deal with them during data analysis [5]. Recently, a panel of experts identified and discussed the challenges of this technique, highlighting the high interlab variability of methodological procedures, which are far from being standardized (Hernandez-Pavon, Veniero et al., Unpublished).

Variability in methodological procedures is common in complex techniques that produce multidimensional data, including fMRI, MEG, and EEG [6,7]. Importantly, such variability can undermine the reliability and reproducibility of results [8]. TMS–EEG is no exception, with methodological variability involving data acquisition and data processing. As an example, varying processing pipelines has been shown to lead to significant changes in TMS-evoked potential (TEP) shape and amplitude [5]. This clearly represents a major challenge that introduces noise in the research field and hinders scientific advancement, with no easy solution given the lack of a ground truth to define optimal methodological procedures.

Direct comparison of data recorded in different labs is a crucial step for understanding whether TMS–EEG signals can be reliably measured across sites and to identify the main sources of variability. However, the currently available literature is insufficient to draw such conclusions. First, compared to other neuroimaging techniques, there are not enough published studies for a systematic investigation of the variables that may affect TMS–EEG signals. Second, most studies are monocentric and characterized by small sample sizes, making them prone to type I and II errors. Moreover, only a small percentage of published papers are associated with an open repository dataset, with a lack of a dedicated standardized data format, e.g., BIDS format, to favor data sharing. Finally, available studies have been highly explorative with little replication both within and between labs.

Inspired by collaborative initiatives that have started in the field of neuroscience (e.g., EEGmanylabs, EEGmanypipelines, Psychological Science Accelerator, Many babies), we have implemented an international collaborative effort called *Team for TMS–EEG* (T4TE). The general aim of T4TE is to improve the reproducibility of TMS–EEG research through high methodological rigor, acquisition of large datasets, scientific transparency and data sharing.

T4TE (Fig. 1) calls for the development of multiple projects, each investigating a defined TMS–EEG outcome measure (e.g., TEPs). This large-scale multicentric approach aims to tackle three crucial issues: 1) validity, i.e., which physiological process each measure represents; 2) reliability, i.e., to what extent each measure is consistently obtained across labs under different recording setups and analysis procedures; and 3) applicability, i.e., can the outcome measures be used as a potentially useful biomarker of pathological conditions.

Studies run within T4TE will include the collection of new multicentric datasets and will follow a defined structure: Any lab will have the possibility to propose a study as a leading lab, defining the TMS–EEG index that will be investigated and which of the three main aims will be addressed (i.e., validity, reliability, applicability). Then, the leading lab will gather participating labs with the support of the T4TE core team, which will promote the study through multiple channels (T4TE website - www.T4TE.org, mailing lists, social networks, etc.). After the definition of the experimental design and protocol, each study will be submitted as a registered report and peer-reviewed prior to data collection. Signal quality checks will be required in each lab participating in data collection. After in principle acceptance, data collection will begin, followed by data analyses and stage 2 submission.

Within this framework, the core team is launching the first study. T4TE-Study 1.1 is focused on TEPs obtained after stimulation

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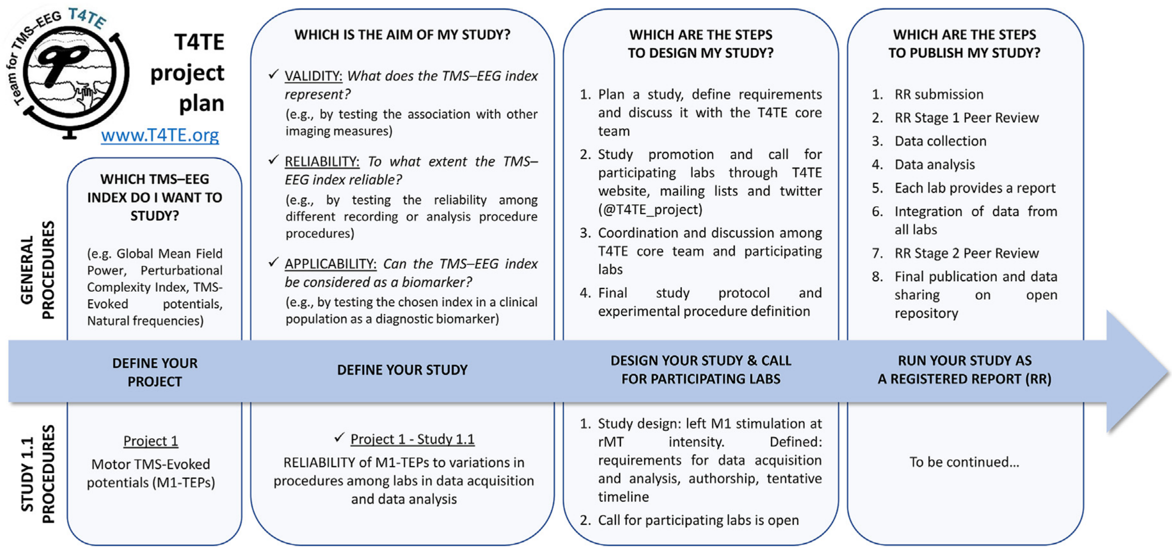

Fig. 1. Flow chart of studies conducted within T4TE. The general structure is depicted on the top of the figure. Studies will be grouped into projects based on the TMS–EEG index under investigation. Each project can then include studies under three aims, i.e., validity, replicability and applicability. We expect that each study will follow the steps reported here. The first study launched by T4TE, Study 1.1, is currently ongoing: it is part of Project 1, and its development is depicted in the bottom part of the figure.

of the primary motor cortex (M1-TEPs). M1-TEPs are among the most studied indexes in the TMS–EEG literature but still present several sources of variability and controversy. The aim is to test the interlab reliability of M1-TEPs, disentangling the effects of data acquisition and data processing. Moreover, T4TE-Study 1.1 aims to investigate the impact of methodological variability on two previously reported effects: a) TEP amplitude modulation in association with high and low cortio-spinal excitability, as indexed by motor-evoked potentials [9]; b) TEP amplitude modulation in association with prestimulus EEG oscillations [10].

By overcoming statistical power issues and fostering collaboration in an open science framework, we expect that this endeavor will benefit the entire TMS–EEG community by significantly increasing reproducibility. This will lead towards a community-wide evidence-based consensus on proper means to collect, analyse and interpret TMS–EEG data.

Declarations of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PJ has received consulting fees from, and shares a patent with Nexstim Plc (Helsinki, Finland). TM has successfully applied for funding for a collaborative research project (project not started at the time of the submission) with Bittium Biosignals Oy (Kuopio, Finland). The other authors have no conflict of interest.

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