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ACES: Automated Correlation of Electric field strength and Stimulation effects for non-invasive brain stimulation

Dear Editor

Multiple sources of (protocol, inter-individual) variability contribute to the limited reliability of non-invasive brain stimulation (NIBS) findings [1]. Meta-analytical techniques could potentially even out such variability, but are hampered by the large parameter space involved [2]. Wischnewski and colleauges [3] recently proposed a partial solution, suggesting a novel approach to aggregate transcranial direct current stimulation (tDCS) studies using various montages and stimulation parameters. They simulated the electric field in a common head model using SimNIBS [4], an open source software which allows the user to model the fields induced by a specific NIBS protocol in a particular head model. The stimulation protocols were hence transformed to sets of merely quantitatively differing values in a common brain space, rendering them directly comparable. Subsequently, the electric field magnitude (|E|) values from these simulations were correlated to the effect sizes across studies, identifying loci where electric field magnitude was associated with an impact on the outcome of interest (i.e., working memory performance). An analogous method could in principle handle inter-subject variability, i.e., overcome morphological differences or aggregate data from different montages at the within-study level (see below).

To facilitate adoption of this approach, we introduce Automated Correlation of Electric field strength and Stimulation effect (ACES), a MATLAB algorithm enabling the aggregation of NIBS findings on the meta-analytical or within-study level. To foster easy adoption, all input can be entered through the MATLAB GUI; no coding skills are required. Apart from user-friendly automatization and minor features, ACES incorporates three principal methodological advancements. First, ACES allows to weight studies for meta-analytical purposes. Second, ACES incorporates a cluster-based method [5] which can handle the spatial contiguity that typically characterises |E|. This approach can retrieve small areas featuring strong associations between |E| and stimulation effect as well as large areas where they are only moderately associated. Third, the cluster-based permutation test implemented in ACES features adequate multiple comparison control. This is critical, given that, typically, tens of thousands of correlations are involved. A detailed practical manual and the algorithm itself can be found here: https://osf.io/5rswh/. Fig. 1 gives a general overview of the procedure.

In a first step, ACES correlates |E| with a quantification of the stimulation effect, across studies or participants. This correlation is computed for each of the elements making up the SimNIBS output mesh. The results is a mesh with a *correlation* per element (performance – electric field correlation or *PEC* [3]). For example, a large PEC at a given site reflects that studies featuring higher intensity stimulation at that location tended to report larger effect sizes. As NIBS effects can be nonlinear [6], ACES supports both Pearson and Spearman's rank correlation, although Pearson might still be preferable in such circumstances [7]. The Spearman correlation is implemented as a Pearson correlation on value ranks with fractional ranking in case of ties. ACES uses the studentized correlation coefficient [8]. For meta-analytical purposes, the precision of individual studies may be important to consider, approximated by sample size, or through more advances weighting schemes. Therefore, ACES can weight studies equally, by sample size, or another precision measure, by means of the weighted Pearson correlation between variables x and y given study weights N:

$$m(x;N)=\frac{\sum_i N_i x_i}{\sum_i N_i}$$

$$cov(x,y;N)=\frac{\sum_i N_i (x_i - m(x;N))(y_i - m(y;N))}{\sum_i N_i}$$

$$corr(x,y;N)=\frac{cov(x,y;N)}{\sqrt{cov(x,x;N)cov(y,y;N)}}$$

As |E| of neighbouring mesh elements differs only gradually, PECs of neighbouring mesh elements are not independent. Cluster-based permutation tests can handle significance testing in the context of such spatial correlation [5], identifying *contiguous clusters* of mesh elements with significant PECs. Thus, in a second step, an arbitrary threshold is used to filter out small correlations and demarcate clusters. Negative correlations are set to zero - if desired, negative correlations can be investigated by inverting the sign of the input effect sizes. Next, *t*-values of above-threshold PECs are summed for each contiguous cluster, to be used for significance testing.

Finally, for the permutation test, effect sizes are shuffled and PECs recomputed, using the same thresholding and clustering procedure as on the observed true PECs. In case of weighting, the correspondence between effect sizes and sample sizes is maintained throughout the permutations. The *maximal* cluster score and maximal individual *t*-value across mesh elements is stored for each permutation. The position of observed (peak or cluster) values in the ordered list of the permuted values is used as a criterion for statistical significance, thus controlling for multiple comparisons [5,8]; e.g., 95th percentile corresponds to a one-sided $\alpha = 0.05$.

ACES outputs a table with cluster size, peak and cluster *t* and *p*, and 3D coordinates of cluster peaks. Analyses on surface meshes can be easily visualized, and we provide example code to automatize this procedure.

While originally developed for meta-analytical purposes, the logic of ACES can be expanded to handle inter-subject variability at the within-study level. If individual anatomical data form participants are available, SimNIBS allows the user to first simulate fields in each unique

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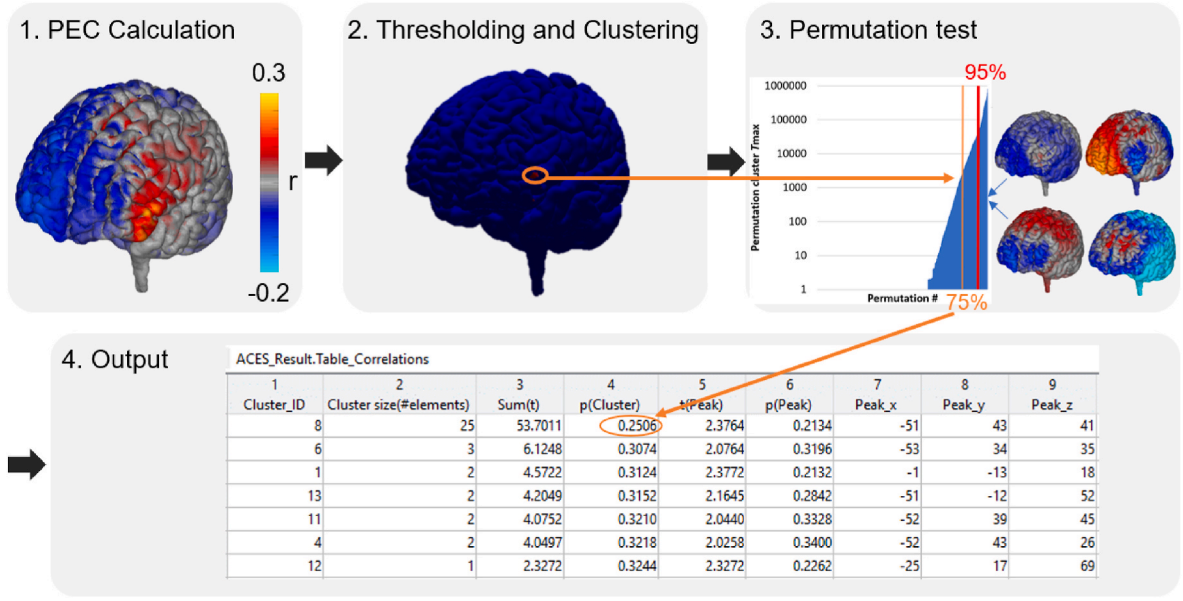

Fig. 1. Graphical outline of the ACES algorithm as applied to the left hemispheric data of Wischnewski et al. (2021), without weighting. Surface mesh input was used for ease of visualization.

participant brain, and subsequently transform the outcome to a common head model for all participants. It is then possible to investigate, at the group level, where in the brain tissue stimulation exerts the strongest effects. Alternatively, one might conceive of single study designs where the impact of different montages on the same outcome is investigated through ACES, e.g. to determine an optimal stimulation site. The ACES manual details one simulated example of this approach.

We have also provided reproducible examples, scripts to automatize visualization of the results, and simulations for demonstration and validation purposes (https://osf.io/5rswh/). Briefly, our simulations demonstrate A) that ACES can pick up spatial associations between field strength and effect sizes; B) that it can suggest an optimal stimulation site based on a body of existing studies none of which directly targeted that particular site; C) the added value of the weighted correlation to improve spatial precision in the context of measurement noise and D) the utility of our cluster-based procedure in avoiding false positives.

Some considerations are critical for valid application of ACES. Many sources of variability cannot be addresses through ACES, e.g., stimulation duration, polarity, number of sessions and rhythm and frequency parameters of tACS and rTMS. Aggregation of data across differences in these parameters should be conducted with great caution. Second, as ACES relies on correlations, it can only retrieve monotonic relationships between |E| and stimulation effects, while other patterns (e.g., inverted U) may be plausible [6]. Third, ACES is insensitive to differences in polarity. Imagine, hypothetically, a treatment outcome entirely dependent on right anodal influence in a set of tDCS studies using the popular F4/F3 montage. If input would be restricted to symmetric/bilateral montages, significant right hemispheric clusters uncovered by ACES would be mirrored by clusters in the left hemisphere. Further, including studies with the opposite montage (left anode) would reduce or obscure the true correlation, as |E| in the right hemisphere would be unchanged, while stimulation effects would be absent for those studies.

A strength of ACES worth emphasizing is its data-driven nature; it doesn't require a priori choices regarding ROIs or summary statistics, which have a significant impact [9].

The ability to extract novel insights through the aggregation of pre-existing datasets hinges crucially on the quality and precision of the initial reports. This implicates general issues such as publication bias but also specific NIBS-related issues. The level of detail that can be incorporated in simulating an E-field in SimNIBS is currently much higher than that what is typically described in method sections. For example the precise orientation of tDCS electrodes can have a substantial impact on the behavioural effects and induced fields [10]. While software like SimNIBS allows the user to incorporate this information in field modelling, it is often not or imprecisely reported.

To conclude, ACES is an easy-to-implement algorithm to aggregate NIBS data in a spatially agnostic manner. By translating qualitative differences in stimulation parameters and individual morphology to quantitative field strength differences in a shared space, the very same variability that currently hampers progress in the field may be leveraged to improve NIBS targeting in the longer run. We welcome all feedback from the community.

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CRediT authorship contribution statement

Kris Baetens: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Data curation, Conceptualization. **Sybren Van Hoornweder:** Writing – review & editing, Software, Methodology. **Taylor A. Berger:** Writing – review & editing, Validation. **Miles Wischnewski:** Conceptualization, Methodology, Resources, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

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