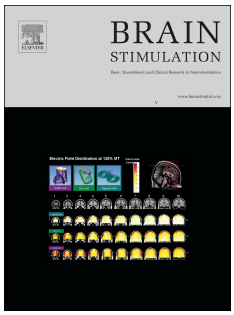
Accepted Manuscript



On the use of meta-analysis in neuromodulatory non-invasive brain stimulation

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PII: S1935-861X(15)00900-6

DOI: 10.1016/j.brs.2015.03.008

Reference: BRS 713

To appear in: *Brain Stimulation*

Received Date: 25 March 2015

Accepted Date: 31 March 2015

Please cite this article as: Nitsche MA, Bikson M, Bestmann S, On the use of meta-analysis in neuromodulatory non-invasive brain stimulation, *Brain Stimulation* (2015), doi: 10.1016/j.brs.2015.03.008.

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In humans, non-invasive brain stimulation (NIBS) can modulate cortical excitability and activity. The buoyant use of this technique in basic and applied research requires further characterization of the basic mechanisms to divorce promising applications from those producing more heterogeneous outcomes. Here we outline some criteria and pitfalls for using published results to gain estimates about the effects of NIBS techniques through meta-analysis and related tools.

Most NIBS studies are currently at phase 1 or phase 2, and address method optimization, test for basic mechanisms of specific NIBS protocols, or apply NIBS as interventional tool for studying structure-function relationships. Meta-analyses across sets of studies can be a valuable tool to identify factors influencing safety or efficacy, but inevitable data

selection and reduction (reducing dimensionality to support a specific hypothesis) warrants tremendous caution. Meta-analyses are intended to overcome within-study biases or idiosyncrasies. However, ignoring intentional methodological variations across studies can lead to spurious conclusions if omitting relevant information that can account for heterogeneity. To our mind, meta-analysis must attempt to be comprehensive and consider all available data; inference on reduced data sets simply can never be better than taking all information into account. The challenge then is to build appropriate statistical and mechanistic models that account for methodological heterogeneity across studies. This approach allows for formalizing all hypotheses about the factors influencing outcomes and effect sizes across different NIBS procedures in a statistical framework. The sophistication of this approach should be no excuse for unnecessary and biased data reduction.

This becomes particularly relevant when considering the vast parameters space for NIBS procedures. Meta-analyses should preferably account for these explicitly in their statistical models, not by pruning the data to a subset of available data. For example, transcranial direct current stimulation (tDCS) dose is determined by electrode montage (location, shape) and waveform applied [1]. While there are several well-established montages for which relatively large datasets are available, a wide range of stimulation parameters has been applied; all these can conveniently be embedded as covariates in meta-analyses. The neurophysiologic, and so presumably behavioral outcomes of NIBS are not necessarily monotonic with stimulation intensity. The outcomes of NIBS are also state-dependent, with even the qualitative direction of outcomes determined by the adjunct task [2]. Inter-individual anatomical and neurophysiologic/pathologic difference will also contribute to variance across experiments. Collapsing across studies without consideration for methodological variations can lead to spurious conclusions - ignoring

optimization details known to influence outcomes (for an overview see e.g. [3]), and whose diagnosis should be a key goal of a meta-analysis. Rather than limiting meta-analyses to a subset of studies that seem to be matched according to some variables of interest, often ignoring relevant other variables, one should build in differences into models of analyses to thereby test which factors do contribute to heterogeneity.

Finally, to make the results of a meta-analysis interpretable and relevant, the procedure has to be transparent, i.e. search criteria, as well as data inclusion and data processing strategies have to be transparent at the single study level. But we also note that full statistics are often not reported in NIBS studies, and effect sizes are relatively rarely described. For making comparisons between studies, and retrospective data analysis easier, reporting this information should become mandatory.

That established forms of NIBS such at TMS and tDCS can change some aspect of brain neurophysiology is well established through clinical and animal studies; the relevant questions relate to mechanisms, optimization, and relation to behavior. Given the state of the field, and the issues explicated above, meta-analyses with the goal of determining a binary conclusion as to if NIBS "works" for some indication, is miscalibrated to the state of the field, and more politics than science. Instead, the field would benefit from critical systematic data analyses that focus on identifying and controlling variables across trials with the goal of optimizing future trials by enhancing reliability, targeted stimulation, and other factors.

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