may have come from the fact that [4] differentiated their data according to 3 different cues – the score we utilized was a pool of all 3.

Price and Hamilton are, however, correct in noting our over-valued *N* with regards to the Sham condition in [4]. Although this paper originally states the Sham group was $N = 45$, they later report that 6 sham participants had to be excluded due to high impedance measures during stimulation, lowering the total to $N = 39$. To determine the impact of this mistake, we have re-run the analysis. Whereas our previously reported effect size for this paper was 0.04 (−0.45, 0.53), the new effect size reflecting the diminished Sham group size is 0.04 (−0.47, 0.55). The new analysis does not change the original conclusion.

Finally, looking over our original paper, we've realized that the references for [4] and [5] in Table 6 have been switched in error. Our apologies for any confusion this typographical error may cause, but this does not affect the analysis.

3) When reporting that only 5 analyses in our paper contain >5 studies, Price and Hamilton mistake *studies* for *authored papers.* As some authored papers contain more than one study, it is important to differentiate the two. In actuality, 12 analyses in our paper contain >5 studies. Price and Hamilton make the same mistake when stating that we included data from 53 studies. In actuality, we report data from 78 studies (any study utilizing both anode and cathode stimulation was only counted once for this value).

Methodological concerns

A primary concern in Price and Hamilton's letter is the lack of reported detail concerning data selection from each study. On this point, we fully agree. Unfortunately, due to space constraints imposed by an already overly-lengthy article (~12,000 words, including Supp.) we were unable to include as much detail as we would have liked. As such, we are grateful for the opportunity to quantitatively address those questions qualitatively raised by Price and Hamilton here.

1) With regards to [6], as noted by Price and Hamilton, the only comparable study [7] provided a single accuracy measure which spanned an online/offline measure. In order to be consistent with this measure, we opted to include Block 4 from [6] – the only block to incorporate both online/offline task measurements. The other option would have been to pool all 5 blocks (1–3 online; 4 online/offline; 5 offline). However, as this was a 'learning' paradigm, there is quite a large discrepancy between earlier and later block performance, meaning pooling will likely dilute any true effect.

However, following Price and Hamilton's comments, we have pooled all 5 blocks and re-analyzed. In the paper, we reported an effect size of 0.18 (−0.46, 0.82). After pooling all 5 blocks, the new effect size is 0.01 (−0.62, 0.65). The new analysis does not change the original conclusion.

2) With regards to [8], Price and Hamilton are correct in pointing out that we only included half the data. The reason for this was because [8] utilized two different visual stimuli for their picture naming task: objects and actions. These authors report a significant difference in the response speed to each category, regardless of stimulation condition. Accordingly, the authors themselves analyzed, presented, and discussed the two streams of data as unique measures. The only comparable study [9] utilized exclusively *object* visual stimuli (no actions). As such, in order to be consistent, we used only the object data from [8].

General concerns

Price and Hamilton raise a general concern involving the small number of comparable studies utilized in many of the analyses. This is a concern we agree with and made explicit in the paper-proper ("… these analyses must be interpreted with caution …" p.14 [1]). Additionally, Price and Hamilton note that there are a small number of studies available and many have small Ns making a robust meta-analysis difficult. Again, we completely agree with this point which is why, throughout the original paper and this letter, we do not use the term meta-analysis to reference our work: rather, we use the term 'quantitative review.'

Conclusion

We welcome and encourage additional analyses utilizing different criteria to develop a deeper, more comprehensive picture of tDCS and its effects. In this particular case, the points raised by Price and Hamilton are based on a misreading of our data selection and use, and re-analysis according to their comments reveals no changes in our original findings.

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On the Use of Meta-analysis in Neuromodulatory Non-invasive Brain Stimulation

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 heterogenous 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 Ref. [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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High-Frequency Anterior Thalamus Stimulation Interrupts Cortical Midline Theta Rhythm During Drowsiness in an Epileptic Patient

Deep brain stimulation (DBS) of anterior thalamic nuclei (ANT) reduces frequency and intensity of epileptic partial and secondarily-generalized seizures [1]. However, exact mechanisms of action and the effects of ANT-DBS on cortical activity are unknown [1]. Midline-theta rhythm during wakefulness and drowsiness is a non-specific electroencephalographic (EEG) rhythm of uncertain significance, seen in a variety of neurologic disorders, including frontal or temporal lobe epilepsies [2]. We report the case of a patient with structural epilepsy and prominent midline-theta rhythm during drowsiness, in which ANT-DBS interrupted reliably and electrode-contact specific this frontal rhythm, similarly to a vigilance increase induced by activating the patient. This is the first direct proof of an acute, electrode-contact specific influence of high-frequency ANT-DBS with standard stimulation-parameters on a cortical rhythm and might be relevant for epilepsies involving frontal cortical regions.