Electrical field based dosing improves non-invasive brain stimulation

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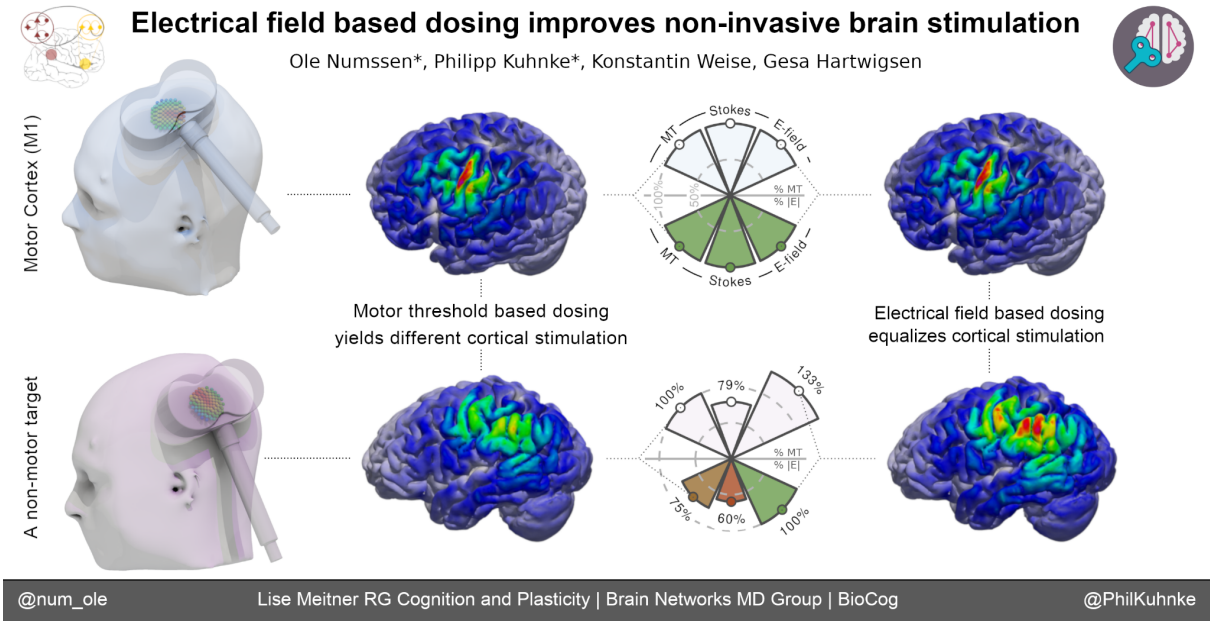

Graphical abstract.

Abstract

Non-invasive brain stimulation (NIBS) methods, such as transcranial magnetic stimulation (TMS), are invaluable tools to modulate cortical activity and behavior, but high within- and between-subject variability limit their efficacy and reliability. Here, we explore the potential of electrical field (e-field) based NIBS dosing to reduce its variability and discuss current challenges as well as future pathways. In contrast to previous dosing approaches, e-field dosing optimally matches the stimulation strength across cortical areas, both within and across individuals. Challenges include methodological uncertainties of the e-field calculation, target definitions, and comparability of different stimulation thresholds across cortical areas and NIBS protocols. Despite these challenges, e-field dosing promises to substantially improve NIBS applications in neuroscientific research and personalized medicine.

Outstanding Questions Box

Outstanding Questions

- Does the cortical threshold for effective stimulation differ between primary regions and higher-level association areas? How large is the impact of cytoarchitectonic differences between regions on a stimulation threshold?
- Do cortical stimulation thresholds differ across individuals? Are thresholds stable within an individual across the lifespan? What are the physiological factors influencing these thresholds?
- Can a cortical stimulation threshold measured with single-pulse TMS be transferred to repetitive TMS protocols for the study of cognition?
- How does the cortical stimulation threshold interact with the current brain state?

Non-invasive brain stimulation (NIBS) techniques, such as transcranial magnetic stimulation (TMS; Pascual-Leone et al., 2000), have emerged as invaluable tools for modulating brain activity in both healthy individuals (Walsh and Cowey, 2000) and neuropsychiatric patients (Burt et al., 2002). Notably, TMS has received FDA approval as a therapeutic intervention for several neuropsychiatric disorders (e.g. O'Reardon et al., 2010). However, high variability of the stimulation effects within and across individuals limits strong conclusions about structure-function relationships (Numssen, van der Burght, et al., 2023; Caulfield et al., 2022). Likewise, the effect sizes in TMS studies are often small (Beynel et al., 2019). Consequently, there is an ongoing debate about the validity and reliability of different TMS protocols in research and treatment settings (e.g. Hartwigsen et al., 2015; Sandrini et al., 2011). Recent studies emphasize that differences in the individual responsiveness to NIBS strongly affect the outcomes and thus explain large parts of the observed variance (e.g., Hamada et al., 2013). One key factor determining NIBS effects, both for primary regions (Sasaki et al., 2018) and cognitive areas (Lee et al., 2021), is the stimulation strength or *dosage*. Currently, the gold standard for dosing across the brain is based on the individual motor cortex excitability and quantified via the motor threshold (MT) (Turi et al., 2021).

Here, we identify shortcomings of the motor-threshold-based dosing approach (MT-based dosing) across various stimulation targets and suggest an alternative strategy. To this end, we present experimental data directly comparing different dosing approaches in the same set of individuals. Critically, standard MT-based dosing strategies fail to consider the actual level of stimulation of the cortical target due to their focus on the *stimulator* intensity (e.g., 50% maximum stimulator output; MSO). In contrast, we highlight the potential of TMS dosing based on the *cortical stimulation* itself, quantified via the induced electric field (Caulfield et al., 2021a; Weise, Numssen et al., 2023; Dannhauer et al., 2022; Kuhnke, Numssen et al., 2023). Throughout this Review, *stimulator intensity* refers to the intensity that is set at the stimulator device (e.g., 50% MSO). In contrast, *stimulation strength* refers to the cortical stimulation exposure, quantified by the e-field strength (e.g., 100 V/m). We

reason that general observations and dosing principles for TMS may also inform other NIBS protocols.

Recent methodological advances have enabled the simulation of the TMS-induced e-fields (e.g. SimNIBS, Puonti et al., 2020, Thielscher et al., 2015; ROAST, Huang et al., 2019), yielding the foundation for a biophysiologically-informed dosing strategy. Calibrating the cortical stimulation exposure to the individual subject and brain region removes a critical variance source of TMS studies: the intra- and inter-individual variability in cortical stimulation exposure due to anatomical differences (Kuhnke, Numssen et al., 2023; Caulfield et al., 2021b). This biophysically-plausible dosing approach potentially extends to other NIBS techniques, such das transcranial electrical stimulation (tES; Kasten et al., 2019; Laakso et al., 2019; Wischnewski et al., 2021) and temporal interference stimulation (Esmaeilpour et al., 2021).
While this is an important step towards more reliable and predictable NIBS outcomes, several crucial links between stimulation intensity and outcome variables remain under-researched, limiting the full potential of this approach. We discuss these issues in detail, including the uncertainties associated with e-field computations and the challenges associated with transitioning from single-pulse to repetitive TMS thresholds. Addressing these knowledge gaps will help unlock the currently unexploited potential of TMS—and potentially other NIBS approaches—for the study of human cognition and the treatment of neurological and psychiatric disorders. Box 1 provides an overview of common implicit assumptions when using MT-based dosing outside the motor cortex.

BOX 1

Common assumptions of TMS dosing based on motor cortex excitability for non-motor areas.

MT- and e-field based TMS dosing individualize the stimulation strength based on motor-cortex excitability. When targeting non-motor regions, such as higher association cortices, with any of these dosing strategies several—usually implicit—assumptions are made about the mechanisms that underlie stimulation effects.

1. **Skin-cortex distance**: MT-based dosing assumes similar skin-cortex distances for the motor hotspot in the primary motor cortex (M1) and the stimulation target. Only for similar skin-cortex distances, cortical stimulation exposures are comparable across targets.

2. **Cortical stimulation thresholds:** All dosing strategies assume similar stimulation thresholds across the cortex, that is, the neuronal tissue at M1 and the stimulation target are assumed to have the same activation functions towards TMS pulses.

3. **Stimulation protocol:** Numerous studies use single-pulse TMS to quantify the motor cortex excitability but apply repetitive TMS (rTMS) to non-motor target areas, for example to modulate cognitive functions. Currently, all dosing strategies assume one global TMS threshold, independent of the temporal dynamics of the stimulation pattern (e.g., single-pulse TMS vs. rTMS).

4. **Outcome measure:** Many studies use similar cortical stimulation intensities (e.g. 100% of the resting motor threshold) to define motor cortex excitability (quantified via motor evoked potentials) and modulate behavioral responses (usually quantified as changes in response speed or accuracy) in cognitive experiments. Here, the same cortical stimulation threshold is assumed across different functional domains and outcome metrics.

Similar rationales apply when using dosing strategies based on other cortical excitability estimates, such as the phosphene threshold in the visual cortex.

Advantages of e-field-based dosing over motor threshold-based dosing

The motor threshold (MT) concept, which originated in the early days of TMS, was intended to standardize TMS effects across subjects and prevent adverse effects from overstimulation by individualizing the stimulation strength (Wassermann, 1998). The MT quantifies the *stimulator* machine output (in % MSO) to yield muscle twitches (motor evoked potentials; MEPs) when stimulating the primary motor region (M1) with single TMS pulses. Despite its motor-centric definition, MT-based dosing is also commonly used for targets outside the motor cortex (Turi et al., 2021). A rationale for this generalization is the lack of a direct output measure to quantify the excitability of most non-motor regions. Critically, however, the *stimulator* output can only provide a rough estimate of the cortical *stimulation* exposure, which drives the cortical stimulation effects and is determined by the e-field magnitude and orientation at the cortex (Numssen et al., 2021). This poses various problems for MT-based dosing, most prominently for targets with a different skin-cortex distance than M1, as cortical areas with a higher distance receive less stimulation for the same stimulator intensity. Likewise, the motor threshold does not correlate with the phosphene threshold (a metric for visual cortex excitability), when quantified via the *stimulator* intensity (Stewart et al., 2001; Boroojerdi et al., 2002). This illustrates that stimulation intensities for non-motor areas based on the motor threshold are somewhat arbitrary. E-field-based dosing approaches aim to solve this issue by normalizing the cortical *stimulation* strength across cortical areas. This can be achieved by computing the induced e-fields for both M1 and the actual target, and then determining the *stimulator* intensity required to produce the same cortical *stimulation* strength at the target area as in M1 at the motor threshold (see Caulfield et al., 2021a for a similar e-field dosing implementation):

Intensity scaling factor = e-field at motor hotspot (in V/m) / e-field at target (in V/m)

*Stimulator intensity (in % MSO) = MT (in % MSO) * Intensity scaling factor*

That is, the e-field strength in M1 at MT is a proxy for the individual *cortical stimulation threshold*—the cortical stimulation strength required to modulate neuronal processing with TMS.

To evaluate the effectiveness and feasibility of e-field based dosing across various cortical targets, we utilized this approach to target different sensory-motor regions as well as higher-level association areas in the left hemisphere (Kuhnke, Numssen et al., 2023). Sensory-motor regions included M1, somatomotor and auditory cortices, while higher-level association regions included the inferior parietal lobe (IPL) and dorsolateral prefrontal cortex (DLPFC), which are common targets in TMS studies of cognition and for clinical applications (e.g. Beynel et al., 2019; Cash et al., 2021). This approach was ideal to elucidate potential advantages and drawbacks of e-field based dosing in comparison to MT-based dosing (e.g., Kuhnke et al., 2020) and other dosing strategies (Stokes et al., 2005).

Standard MT-based dosing applies the same *stimulator* intensity (in % MSO) at all (motor and non-motor) targets. Here, we used 100% resting MT intensity to allow for straightforward comparisons between targets, instead of applying a fraction of MT as frequently done (e.g. 90% or 110% MT; Beynel et al, 2019; Kuhnke et al., 2017). As a second approach, we used an approach proposed by Stokes et al. (2005). This simple heuristic aims to correct for cortical depth differences of motor- and non-motor-targets without assessing on the induced e-field: In Stokes` approach, MT is adjusted by 3% MSO for every millimeter difference in skin-cortex distance between M1 and the target.

Like MT-based dosing and the Stokes approach, e-field based dosing depends on a correct localization of the hand muscle representation to accurately extract the cortical stimulation threshold. To this end, we performed state-of-the-art TMS motor mapping based on ~300 single pulses and motor responses per subject to precisely localize the subject-specific motor hotspot (Weise, Numssen et al., 2022a) for correct e-field extraction. Our three-step protocol utilized pyNIBS v0.3 (Numssen et al., 2021) and SimNIBS v4.0 (Saturnino et al., 2019; Thielscher et al., 2015) to identify

the cortical representation of the index finger muscle. Secondly, we identified the optimal TMS coil positions that maximized the e-field strength in M1 and the other cortical targets ('position optimization'; see Numssen et al., 2021 for details). Thirdly, we calculated the scaling factor for each non-motor target to equalize cortical stimulation exposure across all targets to the cortical threshold determined at M1. For example, a factor of 1.33 for the IPL target translates to a stimulator machine output of 133% of the MT to yield the same cortical stimulation at both targets. Finally, we determined the MT at the optimal M1 TMS coil position.

For M1 stimulation, the three dosing strategies do not differ as this stimulation target provides the common ground for the MT-based and e-field based approaches (Figure 1b & c, left column, Key Figure). M1 is effectively stimulated at 100% MT, leading to a hotspot of high cortical stimulation strength in the precentral gyrus. With MT-based dosing, the same stimulator intensity is simply applied to the other targets (e.g., 100% MT = 39% MSO for our example participant). While this approach seems to work reasonably well for the auditory cortex in this individual, the somatomotor cortex, IPL and DLPFC seem to be understimulated relative to M1 (Figure 1b, top row).

The Stokes approach yields lower stimulator intensities in our example subject for the non-motor targets (e.g., auditory: 77% MT; IPL: 79% MT) as these were located closer to the scalp than M1 (Figure 1b, middle row). Crucially, however, the Stokes approach also leads to understimulation of the non-motor areas in this participant (Figure 1b, middle row). The cortical stimulation exposure does not seem to be better matched between the non-motor targets and M1 than for MT-based dosing. Importantly, e-field based dosing leads to substantially different *stimulator* intensities for the different targets in our example participant (Figure 1b, bottom row). For instance, the somatomotor cortex needs to be stimulated at 146% MT (i.e., 57% MSO) to reach the cortical stimulation threshold for this subject.

Finally, e-field based dosing precisely matches the effective cortical stimulation for the different targets (Figure 1b, bottom row). For each target, e-field based dosing yields a hotspot of high cortical stimulation strength. Comparisons of the *stimulator*

intensity and the cortical *stimulation* exposure identify strong differences between cortical regions (Figure 1c). Only e-field based dosing allows to equalize the *stimulation* exposure across different cortical areas.

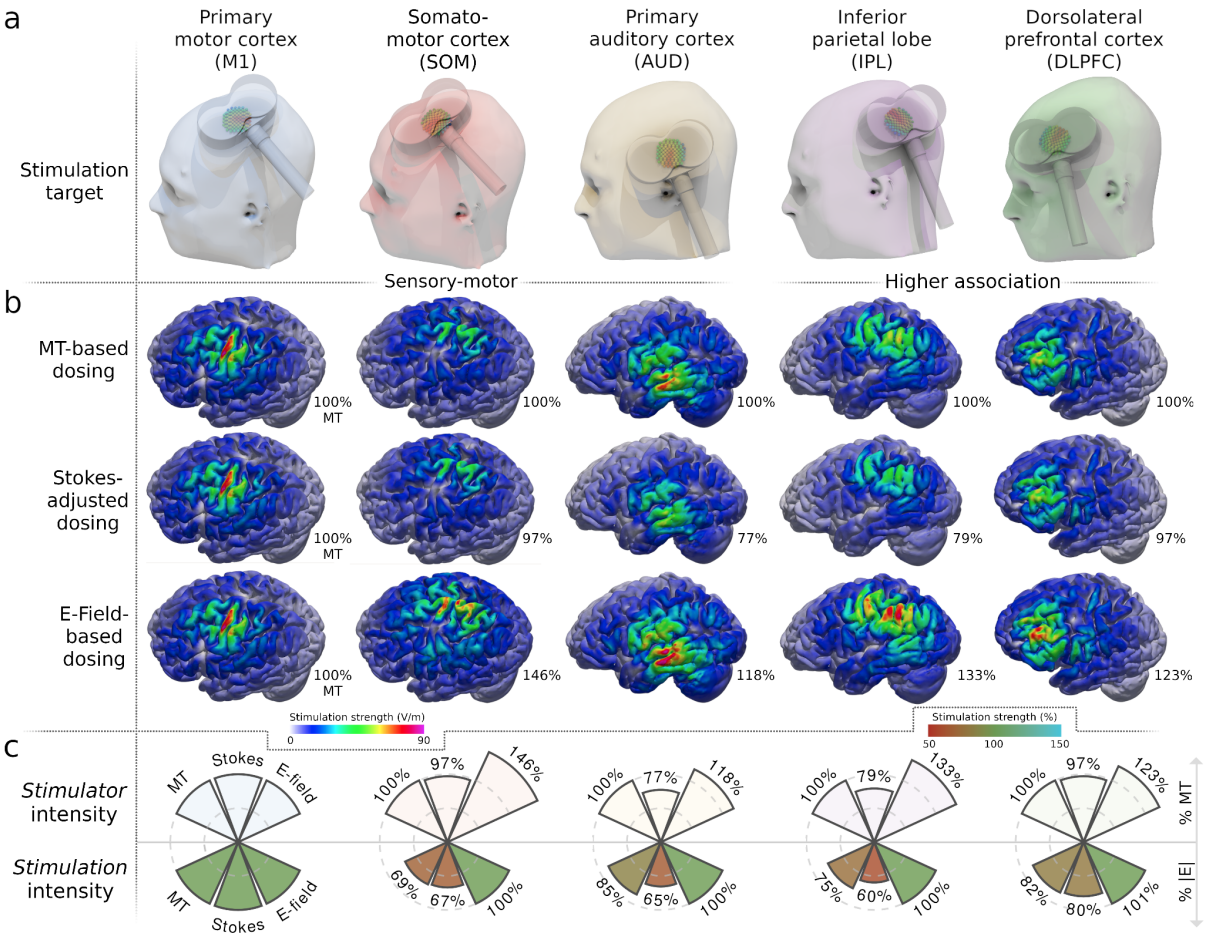

Figure 1. E-field dosing outperforms other dosing strategies on the subject level. (a) All coil placements were selected to maximize the cortical target stimulation. (b) Dosing based on the motor threshold (MT) alone (upper row) applies the same *stimulator* intensity across different cortical target regions (columns), yielding highly variable cortical *stimulation* strengths (quantified in volts per meter; V/m). The "Stokes" method (middle row) linearly adjusts the *stimulator* intensity for coil-to-target distance, but still results in a suboptimal match of cortical *stimulation* across targets. E-field based dosing (bottom row) yields the same cortical *stimulation* strength for all targets. Color: |E|. Percentages: % of MT stimulator intensity. All e-fields are visualized on the gray matter surface for one exemplary subject. (c) The relationship between *stimulator* intensity (upper row) and cortical *stimulation* exposure (bottom row) differs strongly across cortical targets. The *stimulation* exposures were extracted at the cortical targets and related to M1 exposure at MT intensity ('100%').

Results on the group level (obtained from n = 18 healthy volunteers) parallel the central findings from the illustrative single-subject case in Figure 1. MT-based and Stokes-adjusted dosing lead to strong variability of cortical stimulation strengths, both within subjects (across targets) and between subjects (for the same target) (Figure 2). In contrast, e-field based dosing optimally matches the cortical stimulation strength for each target to the respective participant's cortical stimulation threshold—the individual stimulation strength in M1 at MT. This not only minimizes the within-subject variability but also the between-subject variability, so that each cortical target receives the same stimulation strength on average.

The average cortical stimulation threshold across subjects was 59.5 V/m (SE = 2.8) (see *Simulation fidelity* section below for potential limitations of current e-field computations). Most subjects lie between 50 and 70 V/m, with one subject below and two subjects above this range. A detailed analysis of the subjects with a higher cortical threshold revealed that the motor mapping procedure yielded suboptimal fits between e-field and motor evoked potential magnitudes ($R^2 \leq 0.5$). In contrast, the one subject with a significantly lower threshold (~39 V/m) showed an exceptionally good fit ($R^2 = 0.73$). This suggests that cortical thresholds above 70 V/m may reflect suboptimal modeling, rather than genuinely higher cortical thresholds in these participants. Future improvements in e-field modeling, such as refined estimates of the electrical tissue properties will potentially further improve subject-specific cortical threshold estimations (see below).

In conclusion, e-field based dosing better matches the cortical stimulation strength across the cortex than MT-based dosing approaches—both within and across individuals. Therefore, e-field based dosing may increase the stimulation efficacy and reduce both the within- and between-subject variability of TMS effects. Overall, *a priori* e-field simulations promise to substantially improve TMS studies with non-motor targets areas.

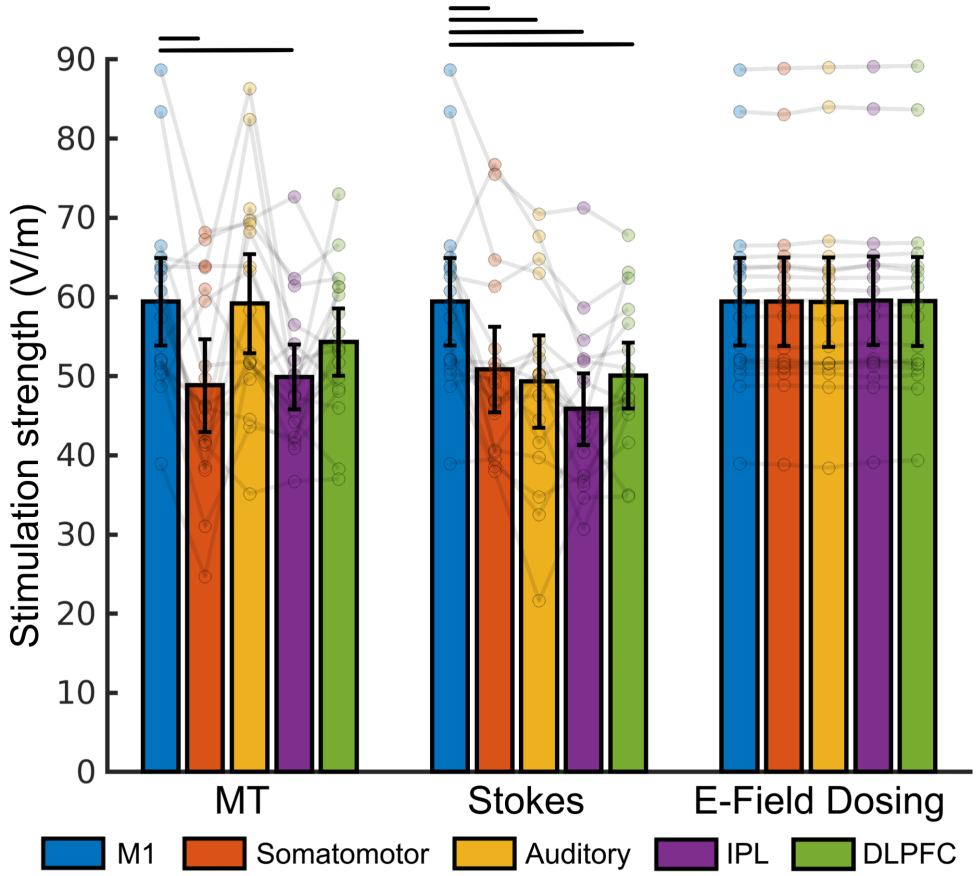

Figure 2. E-field based dosing outperforms other dosing strategies on the group level. The cortical stimulation strength is highly variable for MT-based dosing (left) and Stokes-adjusted dosing (middle), both within and between the 18 participants across the different cortical targets. In contrast, e-field based dosing (right) yields the same stimulation strength for all targets within each participant, which also minimizes the between-subject variability. E-field magnitudes (|E|) were extracted and averaged within spherical ROIs (r = 5 mm) from gray matter volume only. Connected dots show individual subject data; error bars represent the 95% confidence interval. Black bars indicate significant differences ($p < 0.05$; Bonferroni-Holm corrected for multiple comparisons).

Remaining challenges of e-field-based dosing

Despite significant improvements of e-field based dosing from conceptual and methodological perspectives, several challenges in the complex interplay between physiological, methodological, and cognitive parameters (Figure 3) remain to be addressed to unlock its full potential (Box “Outstanding Questions”).

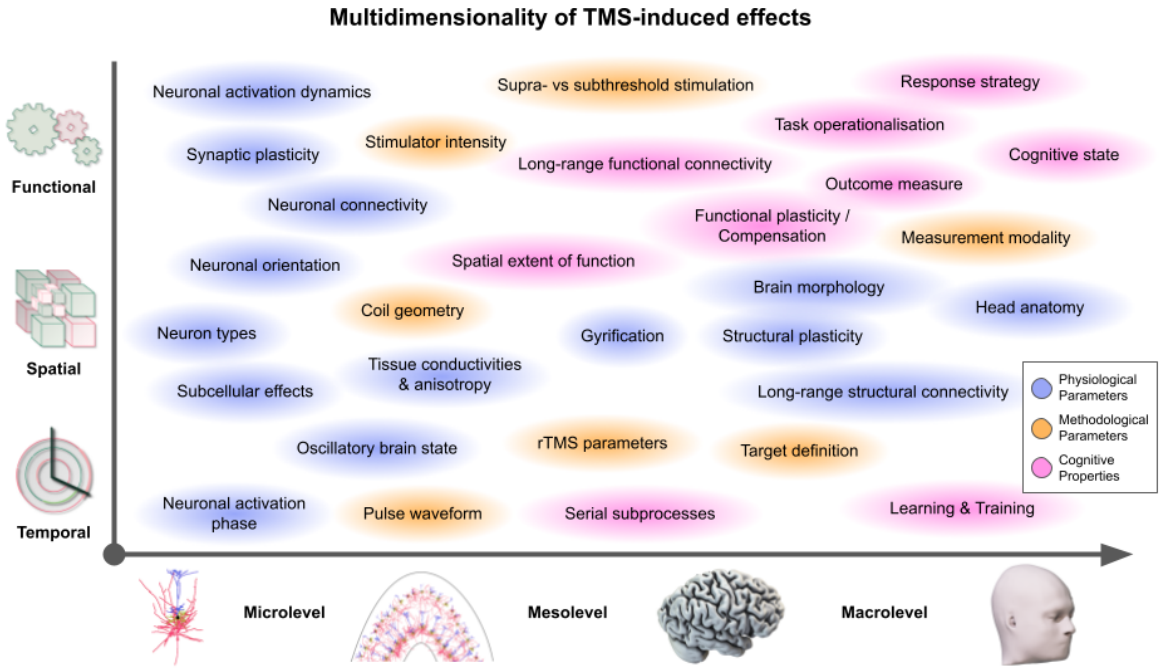

Figure 3. TMS-induced effects depend on a multidimensional set of factors. The outcome of a TMS study (or therapeutical intervention) is the sum of various factors, spanning **physiological parameters** (blue) of the subject (such as gyrification patterns and electric tissue properties), **methodological parameters** (orange; such as pulse waveform and target definition), and **cognitive properties** (magenta; such as response strategies and cognitive brain state). These are defined in the **temporal domain** (*microlevel*: different neuronal activation phases might yield different neuronal responses to a TMS pulse; *mesolevel*: stimulating during different serial subprocesses of a function; *macrolevel*: different levels of training render different cortical target regions effectively), the **spatial domain** (*microlevel*: neuronal orientation towards the induced e-field; *mesolevel*: the TMS coil geometry and gyrification patterns define the induced e-field; *macrolevel*: long-range white matter fiber tracts allow for distal TMS effects), or the **functional domain** (*microlevel*: single-cell activation mechanisms; *mesolevel*: supra- vs- subthreshold stimulation; *macrolevel*: outcome measure, such as response speed vs accuracy).

Simulation accuracy. The development of easy-to-use toolboxes to compute the induced e-fields for individual anatomies and coil placements is still in its infancy and the field has not yet settled on common grounds. For example, the number of relevant tissue types that need to be assessed during e-field computation is still debated (Weise et al., 2022; Weise, Numssen et al., 2023). In addition, although considerable variations of relevant physiological properties such as electric conductivities across subjects and across the lifespan have been reported (Wagner et al., 2004; Antonakakis et al., 2020), these variations are currently not included in

field modeling toolboxes. Approaches to estimate subject-specific tissue conductivities are under development (e.g., magnetic resonance current density imaging; MRCDI; magnetic resonance electrical impedance tomography; MREIT; Göksu et al., 2018; Yazdanian et al., 2020; Eroğlu et al., 2021). Importantly, these variance sources do not necessarily impede within-subject comparisons and e-field dosing based on individualized M1 stimulation thresholds, as these inaccuracies are constant within subjects and within toolboxes. Instead, these limitations affect across-toolbox comparisons and considerations about mesoscopic stimulation mechanistics, which rely on physically correct e-field computations including precise information about the pulse shape. Due to these inaccuracies, the generalizability of individual cortical field thresholds, such as the ~60 V/m presented above, remains to be tested.

Target definitions. E-field based dosing crucially depends on the correct definition of the cortical M1 region-of-interest (ROI) since the effective e-field that yields a neuronal effect is measured at this spot. Specifically, the ROI location and parameters (ROI shape, size, etc.) influence this e-field estimate and the brain stimulation community has yet to settle on common values for both (see Van Hoornweder et al., 2023 for an overview on the different ROI definitions used in TMS studies). Likewise, the “real” cortical target needs to be defined accurately, again, both with respect to its subject-specific location and spatial extent. However, in TMS studies of cognition, the cortical targets are often only roughly defined based on group-level fMRI or even neuroimaging meta-analyses (Beynel et al., 2019), thus introducing inaccuracies when calibrating the e-field. Cortical targets for TMS studies of cognition should ideally be defined using subject-specific fMRI (Sack et al., 2008). Aside from a spatial target definition, the temporal target (Fig. 3, bottom; Romei et al., 2016) also needs to be defined accurately to effectively modulate cortical processing of a specific function, potentially ranging from milliseconds (oscillatory states; Bergmann et al., 2012; Siebner et al., 2022) to seconds (sequential subprocesses of a function; Sack et al., 2005) to even longer time periods (adaptations due to learning and long-term plasticity or compensation; Bergmann & Hartwigsen, 2021).

Different TMS protocols. Besides issues regarding the spatial distribution of the induced e-field, it is worth noting that while the motor threshold is typically assessed using single-pulse TMS, repetitive TMS (rTMS) is commonly employed in most non-motor studies. For example, TMS for major depression therapy utilizes various different protocols, including 1 Hz to 20 Hz rTMS and several variations of theta-burst stimulation (Chen et al. 2013; Teng et al., 2017; Voigt et al., 2021). However, the mesoscopic effects of different rTMS protocols and, thus, their relation to MT thresholds based on single-pulse TMS are currently unknown. To gain a deeper understanding of this relevant issue, modeling approaches will potentially provide valuable insights (see for example NeMo-TMS toolbox; Shirinpour et al., 2021). Currently, *cortical stimulation thresholds* derived from experimental approaches (EEG: 35 V/m to 60 V/m; Rosanova et al., 2009; Zmeykina et al., 2020; EMG: 60 to above 100 V/m; Numssen et al., 2021; Turi et al., 2022; Kuhnke, Numssen et al., 2023) and *neuronal threshold* estimates from modeling approaches (275 to 300 V/m; Shirinpour et al., 2021; Aberra et al., 2020) need yet to converge. Different pulse waveforms, such as mono- vs. biphasic waveforms and steeper vs. longer pulses, add to the different neuronal activation dynamics (Peterchev et al., 2013; Koponen et al., 2018; Zeng et al., 2022). Further research in this area is needed to elucidate the relationships between cortical thresholds for single-pulse TMS and rTMS, particularly in non-motor regions.

Different cortical targets. It is important to note that—besides an assumed similarity between single-pulse TMS and rTMS stimulation thresholds—implicit assumptions of similar cortical responses for different cortical regions are made in (non-motor) TMS studies. For example, the cortical tissue of M1 and IPL differs substantially on the mesoscopic level, with M1 having large amounts of giant Betz cells in layer V and no layer IV, and the IPL showing the opposite pattern (Caspers et al., 2013). Despite this variability of physiological properties, cortical thresholds are currently assumed to be similar across different cortical regions. Most critically, recent modeling approaches have shown that different physiological properties (e.g. Dubbioso et al., 2021) and neuronal types, based on their morphology and orientation within the cortical tissue, show different neuronal activation functions (Aberra et al., 2018,

2020). This questions the assumptions of similarity between cortical regions with respect to transcranial stimulation.

Different functional domains. Finally, in TMS studies of cognition, the existence of a single cortical excitation threshold across different functional domains is assumed implicitly. The motor threshold measures the minimum cortical excitation (with single-pulse TMS of the primary motor region) necessary to elicit MEPs just above the EMG noise floor. However, it remains unknown if the same cortical excitation threshold can be applied to effectively modulate other (cognitive) functions, such as attentional reorienting (Jing et al. 2023) or conceptual-semantic processing (Kuhnke et al., 2020, 2023). As pre-activation of the motor cortex drastically lowers the cortical threshold to evoke MEPs (Rossi et al., 2009), different (cognitive) brain states are also likely to affect stimulation effects within higher association cortices (Silvanto et al., 2008; Feurra et al., 2013; Krause et al., 2022; see Hartwigsen & Silvanto, 2022 for discussion). So far, relationships between functional domains and cortical excitation thresholds remain unknown.

Concluding Remarks

Although e-field based dosing is not a magic bullet for all challenges associated with NIBS studies, it has the potential to substantially decrease across- and within-subject variance of cortical modulation in non-motor studies. By providing a more biologically plausible dosing metric, this approach can play a crucial role in improving the personalization of TMS and tES treatments in clinical settings, as well as increasing the effect sizes of NIBS studies at the group level in research environments. As such, e-field based dosing represents a promising avenue for future research in the field of NIBS.

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