


## Dose-response relationships in transcranial brain stimulation: Physics, physiology and mechanism

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ABSTRACT

The use of noninvasive transcranial brain stimulation methods, such as transcranial electrical stimulation (tES), transcranial magnetic stimulation (TMS), transcranial focused ultrasound stimulation (tFUS), and electroconvulsive therapy (ECT), has grown significantly over the past two decades. Evidence indicates that the dose-response relationship in brain stimulation is neither straightforward nor monotonic, with outcomes influenced by factors such as the brain state, anatomical variability, and neurophysiological mechanisms. Despite advancements in the field, there is still no consensus on standards for estimating and reporting delivered and received stimulation doses or defining dose-response relationships. This paper addresses these gaps by discussing four key areas: (1) factors influencing the delivered dose (stimulation parameters applied at the scalp), (2) quantification of the received dose (electric or acoustic fields delivered to brain tissue), (3) characterization of physiological, behavioral, and molecular responses to specific delivered/received doses, and (4) the dose-response relationship, which describes how variations in dose modulate brain function and behavior. Drawing on evidence from human and animal studies conducted in silico, in vitro, and in vivo, we outline challenges, propose solutions, and summarize current consensus standards. By promoting rigorous methodologies and transparent reporting, this paper aims to advance the reproducibility, safety, and efficacy of research on dose-response assessment in transcranial brain stimulation and its clinical applications.

GLOSSARY

Dose Terms	Explanation
<b>Dose Components</b>	Throughout this review, different types of doses are discussed; in all cases, “dose” refers to a multidimensional set of stimulation parameters, including: <ul style="list-style-type: none"> <li>• Magnitude (e.g., current, magnetic field strength, or acoustic pressure),</li> <li>• Temporal structure (e.g., duration, frequency, phase, duty cycle, and patterning),</li> <li>• Spatial configuration (e.g., electrode/coil/transducer type, size, orientation, and montage or targeting strategy).</li> </ul>
<b>Dose</b>	Refers to the stimulation exposure during a single stimulation event or session.
<b>Dosage</b>	Inspired by pharmacy terminology, it refers to a stimulation regimen that includes the number of sessions and inter-session spacing.
<b>Delivered Dose</b>	The externally applied dose defined at the device or scalp level.
<b>Received Dose</b>	The manifestation of dose components within brain tissue, shaped by individual anatomy and tissue properties.
<b>Recorded Dose</b>	Empirical measurements of one or more received dose components, obtained using physiological recordings, sensors, or in vitro/in vivo experimental methods, and constrained by the spatial and temporal resolution of the measurement technique.
<b>Estimated Dose</b>	Computational model-based estimates of received dose components in brain tissue.
<b>Dose Focality</b>	The spatial component of received dose, reflecting how concentrated stimulation is within brain tissue, defined by the volume or surface area of neural tissue exposed above a specified threshold.
<b>Dose Titration</b>	Systematic adjustment of delivered or received dose components and dosage identify the minimum effective or optimal stimulation exposure.

Response Terms	Explanation
<b>Response</b>	Observable/measurable changes induced by brain stimulation that are defined relative to a comparator condition. <ul style="list-style-type: none"> <li>• <b>Molecular:</b> Cellular or molecular alterations, such as changes in gene expression or protein synthesis, synaptic plasticity, and shifts in neurochemical balance.</li> <li>• <b>Neural:</b> Changes in neuronal activity, excitability, or synchronization, typically assessed using invasive or noninvasive brain mapping methods.</li> </ul>

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Response Terms	Explanation
<b>Comparator</b>	The reference condition against which changes in dose components are evaluated, such as baseline measurements, sham stimulation, or alternative stimulation doses or protocols. The choice of comparator and study design (e.g., within-subject, between-group, or pre-post comparisons) directly influences effect size estimates, inferred dose-response relationships, and responder classification.
<b>Responder</b>	An individual who shows a statistically or clinically meaningful change in an outcome measure relative to a defined comparator condition, according to predefined response criteria.
<b>Population Response</b>	Group-level summary of individual response changes relative to a comparator, capturing effect magnitude, consistency, and responder prevalence.
<b>Cumulative Response</b>	The overall change in an outcome measured over time, capturing the accumulated response to the delivered dose over time.

Dose-Response Terms	Explanation
<b>Dose-Response Relationship</b>	A systematic relationship describing how neural, physiological, or behavioral outcomes change in response to variation in one or more dose components.
<b>Dose-Response Curve</b>	A graphical representation showing how a defined biological or behavioral response varies as a function of one or more dose components, with dose plotted on the horizontal axis and response magnitude on the vertical axis. Dose-response curves may differ across biological levels and outcome measures and commonly exhibit features including: <ul style="list-style-type: none"> <li>• <b>Threshold:</b> the minimum combination of dose components required to elicit a detectable response.</li> </ul>

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Dose-Response Terms	Explanation
	<ul style="list-style-type: none"> <li>• <b>Plateau:</b> a dose range beyond which further increases in dose components produce little or no additional response.</li> <li>• <b>Non-monotonicity:</b> dose ranges in which increasing dose reduces or reverses the response.</li> <li>• <b>Therapeutic Window:</b> the range of dose component combinations that maximize beneficial effects while minimizing adverse or counterproductive outcomes.</li> </ul>
<b>Known Deliverable Dose Range</b>	The set of dose component combinations that can be safely and feasibly applied, constrained by safety guidelines, tolerability limits, and technical feasibility (e.g., device capabilities, electrode/coil/transducer constraints), regardless of whether these combinations produce therapeutic effects.
<b>Therapeutically Effective Dose Range</b>	The subset of the deliverable dose range that produces clinically or behaviorally meaningful benefits, defined by the lowest effective combination of dose components and the highest combination that maintains acceptable safety and tolerability. This range may vary across individuals, brain states, and outcome measures.

## 1. Introduction

Transcranial brain stimulation techniques are widely utilized to modulate brain function and offer non-invasive methods to influence intrinsic brain activity and excitability, leading to lasting changes in brain function [1]. These methods include transcranial magnetic stimulation (TMS) [2], transcranial electrical stimulation (tES) [3], electroconvulsive therapy (ECT) [4], transcranial focused ultrasound stimulation (tFUS) [5], which are the main focus in this paper, and other novel approaches like magnetic seizure therapy [6], and transcranial infrared stimulation [7]. Despite their growing use, a consensus is lacking regarding the estimation and reporting standards for delivered and received stimulation doses, as well as the characterization of dose-response relationships across these techniques. This paper explores the fundamental principles of dose, response, and dose-response relationships in transcranial brain stimulation studies. We aim to review the current principles and methodologies for estimating and reporting dose and dose-response relationships in transcranial brain stimulation while identifying key challenges and potential pathways for advancing research and clinical applications.

## 2. What is dose?

In transcranial brain stimulation, there is a general implicit understanding of the parameters that constitute stimulation exposure. However, there is currently no standardized definition of “dose” across stimulation modalities. In this review, we define dose in transcranial brain stimulation as a multidimensional construct composed of three primary components: (I) magnitude, (II) temporal structure, and (III) spatial configuration, capturing how strongly stimulation is applied, how it is patterned over time, and how it is spatially arranged. Analogous to pharmacology, where the administered drug dose (e.g., in milligrams) differs from the amount of drug that is absorbed and reaches target tissues, transcranial brain stimulation similarly requires a distinction between protocol-defined exposure and tissue-level receipt of stimulation. Accordingly, we distinguish between delivered (administered) dose, defined as the protocol-specified combination of stimulation components applied at the device or scalp level, and received dose, defined as the manifestation of these components within brain tissue (Fig. S1). Importantly, both delivered and received doses comprise all three dose components. These definitions and their operationalization may vary across stimulation modalities (Table 1).

**Table 1**

Comparison of the delivered and received doses definition in different transcranial brain stimulation.

	Mechanism	Delivered Dose	Received Dose
<b>TMS</b>	Brief high-voltage pulses applied to a coil generate rapidly changing magnetic fields that induce electric fields in cortical tissue, triggering neuronal depolarization when activation thresholds are exceeded.	Magnetic field generated by coil current at the scalp, determined by stimulator output, coil type, and positioning.	Induced electric field magnitude and spatial distribution within brain tissue, including the proportion of neurons exceeding firing threshold.
<b>tES</b>	Low-amplitude currents delivered through scalp electrodes generate weak electric fields that modulate neuronal membrane potentials and plasticity without directly evoking action potentials.	Electrical current applied at the electrode–scalp interface, determined by stimulator output and electrode montage.	Electric field magnitude, direction, and distribution within brain tissue, producing subthreshold modulation of neuronal populations.
<b>ECT</b>	High-intensity electrical currents delivered via scalp electrodes induce widespread neuronal depolarization and a generalized seizure under anesthesia, producing large-scale neuromodulatory effects.	Electrical charge and current delivered at the scalp electrodes according to stimulus parameters and montage.	Brain-wide electric fields sufficient to induce seizure activity, including seizure propagation and network recruitment.
<b>tFUS</b>	Focused acoustic waves produce mechanical forces in neural tissue, potentially modulating neuronal activity via membrane displacement, mechanosensitive channels, and secondary neuromodulatory effects.	Acoustic pressure and intensity at the transducer surface determined by ultrasound output and sonication parameters.	Acoustic pressure, radiation force, and particle displacement within brain tissue, with spatially focal mechanical effects.

## 3. What is dosage?

In pharmacology, treatment effects depend not only on total dose but also on the temporal pattern of dose, also referred to as dosage [8]. For example, consuming several alcoholic drinks in a short period leads to intoxication, whereas the same total amount spread over hours may produce minimal effects, highlighting the importance of dose rate in addition to cumulative dose. A similar principle applies to transcranial brain stimulation, in which temporal aspects of dose operate at two scales: within-session temporal structure, reflecting how stimulation is patterned during a single session (e.g., frequency, burst structure, and train duration), and between-session dosage schedule, reflecting how sessions are distributed over time (e.g., number of sessions and inter-session intervals). Single sessions typically produce transient, state-dependent changes in neural excitability, whereas repeated sessions delivered over days or weeks can induce cumulative and longer-lasting plasticity. Moreover, accelerated protocols, in which multiple sessions are administered within short time windows, may engage different neurobiological mechanisms compared with conventionally spaced schedules, even when the total number of pulses or cumulative stimulation energy is equivalent. Thus, treatment responses reflect both session-level dose components and dosage parameters governing inter-session timing, clustering of sessions, and overall treatment duration.

#### 4. What is delivered dose?

As described above, the three main components of delivered dose in transcranial brain stimulation are magnitude, temporal structure, and spatial configuration (see Table 2). Here, magnitude refers to the strength of the output generated by the stimulation device, such as current intensity, electric field at the scalp, acoustic pressure, or electrical charge. Temporal structure refers to how stimulation is programmed over time within and across sessions, including pulse frequency, burst structure, train duration, inter-train intervals, and session scheduling. Spatial configuration refers to how stimulation is arranged across the stimulation apparatus, including electrode or coil configuration, orientation, size, and targeting approach, which together determine the distribution of stimulation at the scalp or device interface.

#### 5. What is received dose?

The received dose reflects how magnitude, temporal structure, and spatial configuration of the delivered dose translate into tissue-level physical fields or waves within the brain and is not determined by stimulation parameters alone. Instead, it is strongly influenced by individual head and brain anatomy and by tissue properties such as electrical conductivity and acoustic transmission. As a result, identical delivered dose protocols can produce substantially different received doses across individuals. At the received dose level, magnitude determines the strength of these fields or forces and whether stimulation is sufficient to induce supra-threshold activation or sub-threshold modulation. Temporal structure determines how these fields are patterned in time, including pulse frequency, burst structure, and repetition, thereby shaping interactions with ongoing neural dynamics and plasticity mechanisms. Spatial configuration determines how stimulation is distributed within brain tissue, and within this dimension, “dose focality” describes the spatial specificity of stimulation, defined as the volume of neural tissue in which the received dose exceeds a biologically relevant threshold (TMS: figure of eight coils:  $\sim 1\text{--}5\text{ cm}^2$ , deep/circular coils:  $\sim 10\text{--}20\text{ cm}^2$ , tES: Conventional tES:  $\sim 25\text{--}35\text{ cm}^2$ , HD-tES:  $\sim 1\text{--}5\text{ cm}^2$ , ECT:  $\sim 25\text{--}100\text{ cm}^2$ , tFUS:  $\sim 0.1\text{--}1\text{ cm}^2$ ).

#### 6. What is recorded/estimated dose?

Because the true received dose within brain tissue cannot be directly measured noninvasively in humans, studies rely on recorded and estimated doses as proxies for tissue-level stimulation. Recorded dose refers to empirical measurements of one or more received-dose components obtained using physiological recordings, sensors, in vitro or in vivo experimental methods, and is constrained by the spatial and temporal resolution of the measurement technique. Estimated dose refers to computational model-based estimates of received-dose components in brain tissue, typically derived by integrating stimulation device parameters with individual anatomical data and tissue properties. Both recorded and estimated doses provide partial representations of the true received dose and may capture different aspects of field magnitude, temporal dynamics, or spatial distribution. As a result, uncertainty in dose measurement and estimation can contribute to variability in observed responses and may obscure true dose-response relationships, highlighting the importance of improving both empirical measurement techniques and biophysical modeling approaches.

#### 7. What is response?

In transcranial brain stimulation, response refers to observable or measurable changes induced by stimulation that are evaluated relative to a specified comparator condition, such as baseline, sham stimulation, or an alternative protocol or parameters. Responses arise from the interaction between participant-specific factors, including anatomy, brain state, and pathology, and stimulation parameters such as intensity,

**Table 2**  
Delivered dose parameter space in transcranial brain stimulation.

	Delivered Dose Variable name	Definition/Example	
TMS	Magnitude	Stimulation intensity	% of resting/active motor threshold, % maximum stimulator output corresponding to the maximum current flow through the coil e.g., 1.5T, 3T
		Magnetic field strength (Tesla)	
	Spatial Configuration	Coil type	Figure-eight, circular, double cone, H-coil
		Coil orientation	Relative to skull/specific brain area
		Coil positioning	Motor hotspot, neuronavigation-based, scalp measurement
		Targeting method	Anatomical, functional, personalized fMRI/EEG guided
	Temporal Pattern	Frequency (Hz)	1 Hz, 10 Hz, 20 Hz, 50 Hz, theta burst 5 Hz
		Inter-train interval (seconds)	for rTMS, iTBS, cTBS, patterned protocols
		Pulse shape	Monophasic, biphasic
		Number of pulses per train	for rTMS, and patterned protocols
Total number of pulses		Cumulative number of pulses in each session	
Inter-session interval		Single-session vs. multiple-session	
tES	Magnitude	Stimulation mode	Continuous, intermittent, task-related
		Total number of sessions	Cumulative number of sessions in accelerated trials
	Spatial Configuration	Current intensity (mA)	Absolute (peak-to-peak) stimulator output
		Current density (mA/cm <sup>2</sup> )	Stimulation intensity accounts for electrode size
		Electrode configuration	Stimulating/return electrode location and orientation
		Electrode size and material	e.g., 5 × 7 cm sponge with 2 mm thickness, rubber, saline-soaked
	Temporal Pattern	Electrode impedance ( $\Omega$ , k $\Omega$ )	Electrode-skin impedance
		Stimulation duration (minutes)	Total duration of the stimulation
		Polarity	for tDCS: anodal/cathodal; for tACS: in-phase/out-of-phase
		Waveform characteristic	Frequency (Hz), Phase, Shape (e.g., sinusoidal, square, random noise)
Magnitude	Total number of sessions	Cumulative number of sessions in multi-sessions trials	
	Charge dose (mC)	Calculated based on percent above seizure threshold (current x pulse duration x number of pulses)	
ECT	Spatial	Energy (J)	Total electrical energy delivered to the patient (voltage x current x pulse duration x number of pulses)
		Pulse intensity (mA)	Amplitude of the stimulator output e.g., RUL, BL, bifrontal, FEAST
		Electrode configuration	
	Temporal Pattern	Electrode size and material	e.g., circular (r = 5 cm) sponge, rubber, saline-soaked
		Pulse characteristic	Frequency (Hz), Pulse width ( $\mu$ s)
		Train duration (second)	Total pulse train time
	Seizure duration	Seconds, EEG-monitored	
	Total number of sessions	Cumulative number of sessions in multi-sessions trials	

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Table 2 (continued)

Delivered Dose Variable name		Definition/Example	
tFUS	Magnitude	Ultrasound frequency (kHz/MHz)	e.g., 250 kHz–1 MHz
		Intensity (ISPPA, ISPTA, mW/cm <sup>2</sup> )	Spatial-peak pulse-average intensity
		Peak negative pressure (MPa)	Determines cavitation risk
	Spatial Configuration	Transducer geometry, type, position	Single-element, phased-array
		Coupling medium	e.g., water, gel, degassed medium
		Targeting approach	Structural MRI, neuronavigation, skull correction
	Temporal Pattern	Duty cycle (%)	Continuous vs. pulsed ultrasound
		Pulse repetition frequency (PRF)	In Hz
		Duration of stimulation (minutes)	Cumulative duration of the stimulation
		Sonication characteristic	Sonication duration (ms), Inter sonication interval (ms-sec)
	Total number of sessions	Cumulative number of sessions in multi-sessions trials	

frequency, and duration, and can be characterized across multiple biological levels. At the most proximal level, molecular responses involve cellular and synaptic alterations, including changes in gene expression, protein synthesis, synaptic plasticity, and neurochemical balance. These molecular processes can translate into neural responses, reflected in changes in brain activity, excitability, and network synchronization, typically measured using neuroimaging or electrophysiological techniques. Downstream of these neural effects, physiological responses capture neural-mediated bodily changes, such as motor-evoked potentials, autonomic function, and neuroendocrine markers. Ultimately, these biological changes may manifest as behavioral and clinical responses, including changes in task performance, observable behavior, symptoms, or subjective experience.

## 8. What is a dose-response relationship?

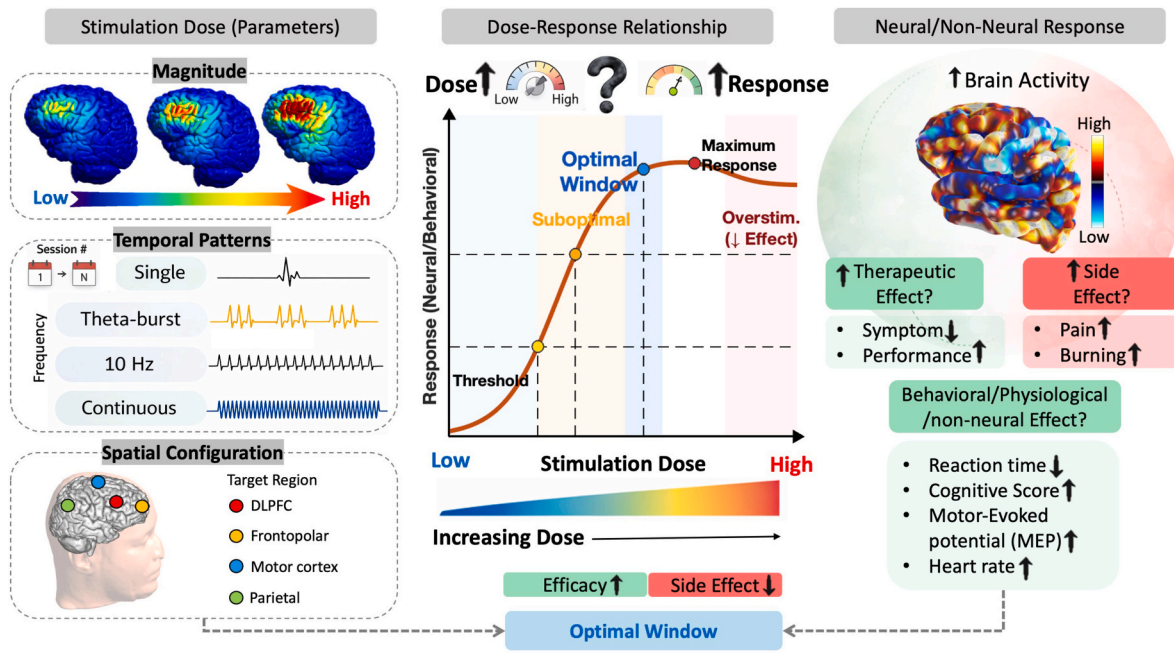
In pharmacology, dose–response relationships describe how the magnitude of a biological response changes as a function of drug dose and are typically modeled as mathematical functions or curves [9]. Most pharmacological dose–response curves are monotonic and sigmoidal, often described by the Hill equation [10–12]. Therapeutic use is further constrained by adverse effects, with the range between effective and toxic doses defining the therapeutic window and the maximum tolerated dose [13]. These principles provide a useful conceptual framework for neuromodulation, but they do not directly translate to transcranial brain stimulation. Unlike pharmacological agents, where dose is often represented by a single concentration or amount, stimulation dose is inherently multidimensional and depends jointly on magnitude, temporal structure, and spatial configuration of the applied fields or waves. Consequently, responses in transcranial brain stimulation reflect interactions among multiple components of the delivered and received dose rather than simple monotonic relationships with any single parameter. In this context, the dose–response relationship describes how molecular, neural, physiological, or behavioral outcomes change as a function of systematic variation in one or more dose components, and is therefore better conceptualized as a multidimensional response surface rather than a one-dimensional curve, requiring experimental designs and computational models that explicitly account for interacting dose dimensions. Despite this, most neuromodulation studies rely on low-dimensional parameter sweeps and conventional statistical models that are poorly suited for capturing interactions, non-linearities, and trade-offs across dose dimensions. The

lack of scalable experimental designs and multivariate modeling frameworks has limited rigorous characterization of multidimensional dose–response surfaces, impeding principled dose optimization and cross-study synthesis. This conceptual framework, including the interaction between dose dimensions (magnitude, temporal, and spatial) and the resulting non-linear biological outcomes, is illustrated in Fig. 1.

## 9. Dose quantification in dose-response relationship

Because these tissue-level fields and waves cannot yet be measured directly and noninvasively in humans, computational modeling is the primary approach for estimating received dose by integrating stimulation device properties, protocol parameters, individual anatomical data, and tissue conductivity to generate individualized estimates of field magnitude, temporal characteristics, and spatial distribution. However, the received dose estimation depends on a clear understanding of its limitations and underlying assumptions. Two elements are especially pertinent in this context.

- 1) The simulated fields and waves provide quantitative predictions of delivered dose, but they do not predict the physiological impact of stimulation. Identical delivered and received doses can produce markedly different physiological responses across individuals, across brain states, and across targeted brain regions. For example, interleaved TMS–fMRI studies in healthy participants have shown strong inter-individual variability in intensity–response profiles even when stimulation parameters are identical, with some participants exhibiting linear, threshold, or inverted-U responses to the same dose levels [14,15]. The spatial component of the delivered dose also modulates stimulation efficacy. In TMS studies, dose–response effects based on absolute intensity emerged only when stimulation was delivered at functionally optimized targets, whereas stimulation at standard scalp locations or when dose was normalized to motor threshold failed to show systematic scaling, demonstrating that brain area and network engagement critically shape effective dose [16]. Likewise, interleaved TMS–fMRI studies have shown that intensity effects differ across hemispheres and cortical targets and can habituate across repeated blocks despite constant stimulation parameters, reflecting interactions between spatial targeting and temporal exposure [17]. Consequently, relating electric field modelling to physiological or behavioral outcomes remains unclear and context-dependent, highlighting the need for integrated multiscale models that connect field simulations to neural population and network dynamics to improve mechanistic interpretability and generalizability [18].
- 2) The calculated dose is an estimate of the unknown true tissue-level exposure, and inaccuracies in computational models can limit the reliability of dose–response analyses. Current anatomical head models are typically derived from magnetic resonance images with approximately 1 mm<sup>3</sup> resolution and often assume homogeneous tissue properties, despite known spatial variability in tissue microstructure and conductivity. Consequently, uncertainty arises from anatomical segmentation, assignment of tissue properties, and the modeling and placement of stimulation devices. For example, simulation accuracy is influenced by the type of anatomical imaging used for model construction, with studies demonstrating that segmentation pipelines incorporating both T1- and T2-weighted magnetic resonance images yield more accurate tissue classification and electric field estimates than T1-only approaches [19,20]. Moreover, differences across simulation software packages and segmentation workflows can produce systematic variation in predicted field distributions [21]. However, comparison between intracranial measurements in patients and electric field models, demonstrate moderate to strong agreement between predicted and measured electric field [22]. Additional studies in patients, post-mortem



**Fig. 1. Conceptual schematic of the dose–response relationship in noninvasive brain stimulation.** The figure illustrates how stimulation dose, defined by magnitude (intensity), temporal pattern (e.g., single pulses, theta-burst, continuous stimulation), and spatial configuration (target location), influences neural, physiological, behavioral, and clinical responses. The central panel depicts a nonlinear dose–response curve characterized by a threshold for measurable effects, an optimal therapeutic window associated with maximal efficacy, and potential overstimulation leading to diminished benefit or adverse effects. Increasing stimulation dose modulates brain activity and downstream outcomes, including therapeutic improvements as well as possible side effects. Together, the schematic highlights the multidimensional nature of stimulation dose and emphasizes the importance of identifying individualized optimal dosing parameters.

human tissue, and non-human primates further support the general validity of model-predicted field patterns [23,24].

## 10. Response quantification in dose–response relationship

Although responses to transcranial brain stimulation can be observed at multiple biological levels, the characterization of dose–response relationships depends strongly on how responses are measured. Different outcome measures vary in spatial and temporal resolution, sensitivity to stimulation parameters, and proximity to underlying biological mechanisms, and may therefore yield different apparent dose–response patterns for the same stimulation protocol. Interpreting dose–response relationships thus requires careful consideration of the measurement domain and its methodological limitations.

### 10.1. Neural responses using brain mapping tools

Electroencephalography and magnetoencephalography (M/EEG) provide millisecond-level temporal resolution but comparatively limited spatial precision (~1–3 cm), capturing synchronized activity of neural populations—primarily from cortical pyramidal cells—via oscillatory power, event-related potentials (ERPs/TEPs), event-related oscillations, and connectivity metrics. These methods are particularly sensitive to temporal structure and intensity-related dose components, and are well suited to detect rapid, state-dependent neural effects of stimulation. However, interpretation requires careful control of stimulation-related artifacts and peripheral co-stimulation, especially for TMS–EEG. Consistent with this, studies combining TMS with EEG or fNIRS show that neural responses can vary nonlinearly with intensity, often peaking at intermediate levels and flattening or reversing at higher doses, with dose–response effects being component-specific across evoked and oscillatory measures [25,26]. Moreover, paradigms manipulating both intensity and temporal summation (e.g., number of pulses) demonstrate significant interaction effects, indicating that neural dose–response relationships frequently reflect combined contributions of magnitude and

temporal structure rather than simple monotonic scaling with a single parameter [27].

Functional magnetic resonance imaging (fMRI) provides high spatial but lower temporal resolution and quantifies stimulation-related neural effects indirectly via blood oxygenation level–dependent (BOLD) signals or perfusion measures such as cerebral blood flow (CBF). Concurrent stimulation–fMRI paradigms enable mapping of dose–response relationships at regional and network levels, including both local target engagement and remote network propagation [28,29]. Early TMS–fMRI and PET studies reported stronger local and network-level responses when suprathreshold stimulation was compared with subthreshold intensity, operationalizing dose primarily as stimulation intensity (%MT or MSO) [30,31]. More recent interleaved TMS–fMRI studies using multiple intensity steps demonstrate both group-level intensity effects and substantial inter-individual variability, with participants showing linear, threshold, or inverted-U response profiles to identical delivered-dose manipulations [14,15]. Paired-pulse TMS–fMRI further indicates that dose–response relationships can be spatially specific and nonlinear, with maximal suppressive effects in premotor regions occurring at intermediate intensities [32]. In tDCS–fMRI and perfusion studies, neural dose–response relationships have primarily been linked to current intensity (mA) and montage-dependent field distributions, often supported by coupling at different levels between modeled electric field magnitude and physiological responses [33], rather than to stimulation duration alone. For example, intensity-dependent CBF changes have been reported across wide intensity ranges (e.g., 0.1–4 mA), with effects localized to perirolandic and premotor regions under specific montages [34]. Other multimodal studies varying intensity (0.5–2.0 mA), polarity, and montage demonstrate that CBF and BOLD responses covary with modeled electric field strength across voxels, supporting a received-dose interpretation of physiological effects [35]. By contrast, under certain intermittent temporal delivery patterns, increasing nominal current does not necessarily produce monotonic increases in CBF, underscoring that temporal structure can modulate or mask apparent magnitude-based dose–response relationships [36]. In

tACS–fMRI studies, even when nominal intensity and duration are held constant, inter-individual variation in modeled electric field strength and spatial targeting predicts neural responses, indicating that dose–response relationships may be better captured in terms of received dose at the network level rather than administered current alone [37].

### 10.2. Neural responses using *in-vivo* recording

Single, paired, and multi-cell whole-cell recordings provide direct measurements of excitatory and inhibitory synaptic properties (e.g., amplitudes, synaptic failure rates, paired-pulse properties, and short-term plasticity [38,39]), network connectivity motifs [40], and intrinsic cellular properties [41]. Consistent with dose-dependent neural modulation, invasive recordings in rodents and non-human primates demonstrate that stimulation magnitude can systematically alter neuronal excitability and network responses. For example, in rodent tFUS studies, increasing acoustic intensity produced progressively stronger suppression of TMS-evoked motor responses and longer-lasting inhibitory effects, indicating graded neural modulation as a function of acoustic dose [42]. In cerebellar LIFU experiments combining calcium imaging with electrophysiological measures, both the proportion of responsive Purkinje dendrites and calcium signal amplitude increased with higher intensities, whereas behavioral triggering depended more strongly on stimulation duration, demonstrating dissociable magnitude- and duration-dependent neural thresholds [43]. Similarly, hemodynamic and neural activity changes in mouse motor cortex showed monotonic scaling with both acoustic intensity and sonication duration, while duty cycle exerted weaker influence over the tested range, further highlighting parameter-specific dose sensitivity [44].

These methods are invaluable for assessing the immediate effects of distinct stimulation protocols at the level of individual neurons and their connections. However, they are technically demanding, particularly multi-cell whole-cell recordings, and challenging to apply *in vivo*. These limitations underscore the difficulties in extrapolating laboratory findings to more complex living systems. Understanding how these synaptic and network responses translate to clinical outcomes in humans is further complicated by scaling effects and inter-individual variability. Advances in multi-electrode recordings with high-density arrays now allow for the assessment of local field potentials and single-unit recordings with high temporal and spatial resolution, both *in vitro* and *in vivo* [45]. However, these probes require optimization to minimize artifacts during exogenous electrical stimulation, such as single-pulse or repetitive TMS. Flexible brush-like arrays based on carbon fibers [46] represent a promising approach to enable systematic and artifact-free assessments of dose–response relationships. Additionally, experimental platforms that deliver spatiotemporally uniform electric fields with precisely engineered magnitudes, free from toxic electrochemical by-products, are crucial for improving translation to clinical settings. Microfluidic chambers provide a modern, simple solution for electrically stimulating explanted murine and human brain tissues, integrating electrophysiological recordings with functional optical imaging [47]. Addressing these technical challenges will improve the reliability of translating lab-based findings into therapeutic applications, bridging the gap between experimental data and clinical efficacy.

### 10.3. Physiological and behavioral/clinical response

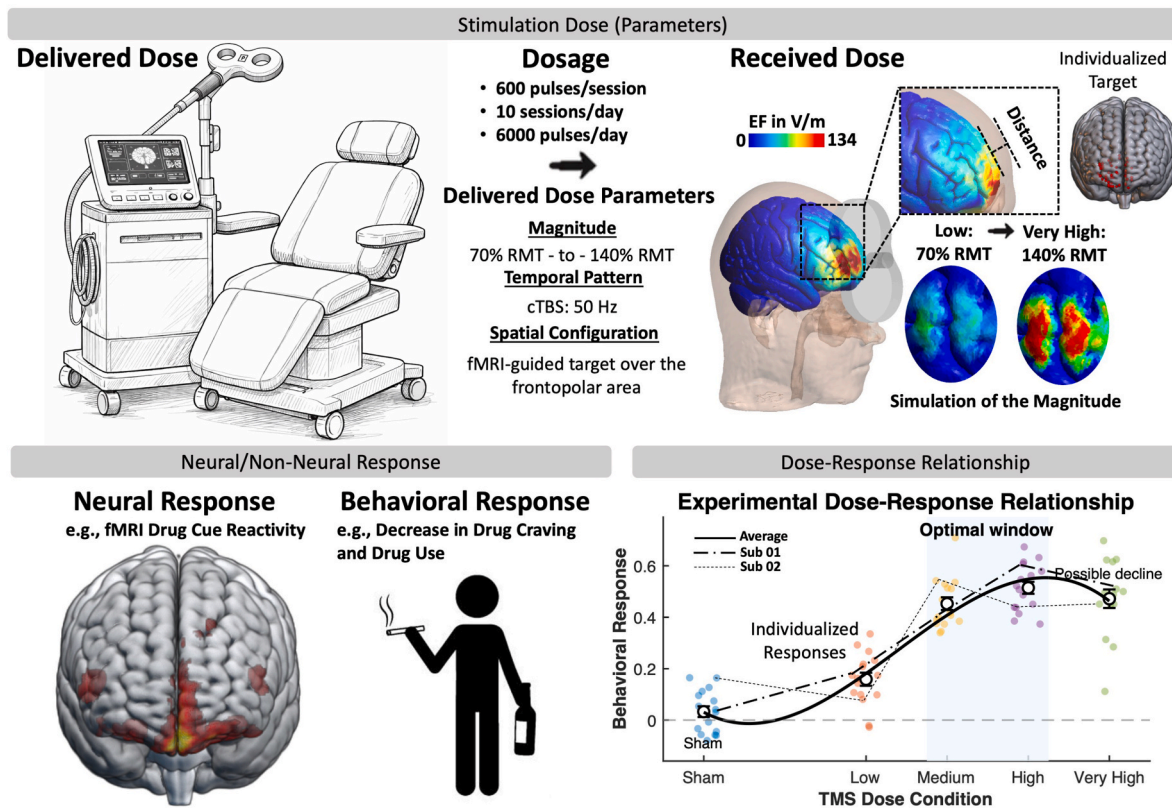
Behavior-based dependent measures are the most common outcomes in neuromodulation experiments, encompassing motor and sensory functions, emotional arousal, and decision-making metrics. TMS, for instance, induces dose-dependent effects beyond simple motor evoked potentials, such as delays in voluntary movement execution, sensory perception alterations, and changes in decision-making processes. These effects help elucidate how varying stimulation intensities and frequencies modulate behavior. A single pulse of TMS over the motor cortex reliably induces a hand contraction at threshold doses,

illustrating an immediate dose–behavior relationship. However, for most brain targets and experimental paradigms, multiple pulses of stimulation are required to observe behavioral changes. This highlights the critical role of behavioral outcomes, as interventions that fail to elicit behavioral modifications—whether in clinical symptoms or everyday functionality—are of limited therapeutic value, even if neural activity changes are observed in fMRI, EEG, or MEPs. In ECT, bilateral electrode placement remains the gold standard for efficacy but causes greater cognitive side effects. Unilateral placement, typically on the right side, minimizes cognitive effects while maintaining efficacy at higher doses relative to the seizure threshold. The bifrontal placement provides a middle ground between efficacy and side effects. A single ECT session often causes temporary memory loss, but 12 or more sessions are typically needed for full therapeutic effects on depression. Such findings demonstrate the significance of exploring stimulation effects on both neural activity and behavior. Ultimately, neuromodulation aims not only to achieve therapeutic behavioral changes but also to deepen our understanding of how stimulation influences neural and behavioral processes, providing a foundation for future clinical and research advancements.

Evidence across neuromodulation modalities indicates that dose-dependent physiological or neural effects do not necessarily translate into proportional behavioral or clinical benefits. In this context, mechanistic linkage refers to the extent to which the neural or physiological processes directly modulated by stimulation lie on the causal pathway to the specific clinical or behavioral symptoms the intervention is intended to modify, while outcome selection refers to the choice of response measures used to index stimulation efficacy. A mismatch arises when stimulation reliably alters measurable biological signals that are not causally sufficient to drive improvement in the targeted symptoms. For example, in a physiological ECT study in patients with major depressive disorder, increasing stimulus charge above seizure threshold produced strong dose–response scaling of autonomic and neurochemical markers, including plasma catecholamines and blood pressure, whereas seizure duration and clinical symptom improvement did not correlate with stimulus dose [48]. Similarly, in a large ECT–MRI cohort, individualized modeled electric field strength (received dose) was positively associated with regional brain volume changes—most robustly in the hippocampus and amygdala; yet neither electric field magnitude nor structural plasticity measures predicted clinical improvement after accounting for covariates [49]. Together, these findings demonstrate that biologically measurable dose–response relationships at molecular, physiological, or structural levels can be dissociated from therapeutic outcomes, even when stimulation effects are robust and reproducible. Such dissociations suggest that many commonly used neural or physiological markers, while sensitive to stimulation dose, may be mechanistically distal from the circuits and computations that generate the symptoms of interest, limiting their utility as surrogate endpoints for clinical efficacy. Addressing this gap therefore does not require expanding outcome measures indiscriminately, but instead calls for aligning outcome selection with the hypothesized mechanism of action, prioritizing response measures that are causally closer to the neural circuits underlying the *a priori* defined therapeutic targets of the intervention. Such alignment is essential for interpreting dose–response relationships and for distinguishing biological engagement from clinically meaningful efficacy in transcranial brain stimulation (see Fig. 2 as an example).

### 10.4. Non-neural response

Although transcranial brain stimulation methods are commonly interpreted as acting primarily through direct modulation of neuronal excitability and firing, increasing evidence indicates that non-neuronal cells, including astrocytes, microglia, neural stem, and oligodendrocyte-lineage cells, also contribute to stimulation effects [50, 51]. Non-neuronal mechanisms include astrocytic calcium signaling [52], microglial modulation of inflammatory and synaptic pruning



**Fig. 2.** Conceptual example illustrating the dose–response relationship in transcranial magnetic stimulation (TMS) for substance use disorders. The top panel depicts the delivered dose, defined by stimulation parameters including magnitude, temporal pattern, and spatial configuration. In this example, delivered dose magnitude changes from 70% to 140% of the resting motor threshold (RMT), delivered using an intermittent theta-burst stimulation (iTBS) pattern (50 Hz bursts repeated at 5 Hz) over the Fp2 location of the EEG 10–20 system. An accelerated dosage schedule is illustrated (600 pulses per session, 10 sessions per day; 6000 pulses/day). The received dose represents the electric field (EF) induced in the brain, estimated using computational head models and influenced by anatomical factors such as distance between the coil and cortex. The lower panels depict response measures, including neural responses (e.g., modulation of drug cue-reactivity measured with fMRI) and behavioral responses (e.g., reductions in drug craving and substance use). The rightmost panel illustrates a hypothetical experimental dose–response relationship, where behavioral improvement (e.g., reduction in drug craving) varies across delivered stimulation dose magnitude, suggesting a potential optimal therapeutic window and possible decline in response at excessively high stimulation doses with interindividual variability across a population.

processes [53], stimulation-associated neurogenesis [54], and activity-dependent oligodendrogenesis contributing to white-matter plasticity, with additional contributions from vascular and blood–brain barrier signaling pathways (e.g., vascular endothelial growth factor and nitric oxide) [55]. However, the magnitude, timing, and functional relevance of these non-neuronal contributions remain poorly quantified, and current evidence does not permit reliable separation of neuronal and non-neuronal contributions to physiological, behavioral, or clinical responses, nor are there established dose–response relationships linking delivered or received dose to cell-type-specific biological endpoints [56,57]. As a result, it remains unclear under which conditions, for which stimulation protocols, and at what scales non-neuronal mechanisms meaningfully contribute to observed effects. Consequently, most existing dose–response frameworks appropriately remain anchored to neuronal and network-level readouts, while non-neuronal pathways are best viewed as potential modulators whose importance likely varies across stimulation parameters, timescales, and outcome domains. Clarifying when these mechanisms are negligible versus when they are consequential—rather than assuming their universal relevance—represents a key challenge for developing biologically grounded and interpretable dose–response models in brain stimulation.

### 11. Inter-individual variability in dose-response relationship

A major source of inter-individual variability in responses to stimulation arises from differences in received dose and the physiological

state of the targeted neural population at the time of stimulation [58, 59]. Received dose reflects how delivered magnitude, temporal structure, and spatial configuration of the delivered dose translate into tissue-level field strength, timing, and spatial distribution, which are strongly influenced by head and brain anatomy, tissue properties (e.g., conductivity), and gyral geometry. Beyond these physical factors, the activation state of the targeted neural population, including baseline excitability and ongoing oscillatory dynamics, critically determines its response to stimulation. As a result, identical stimulation protocols can produce markedly different neural, physiological, and behavioral effects depending on whether stimulation is applied to neurons that are near threshold, rhythmically synchronized, or relatively quiescent. These factors underscore why identical stimulation protocols can yield divergent outcomes across individuals and highlight the need to account for both received dose and neural activation state when interpreting or optimizing stimulation effects [60] like what can be achieved in neuroimaging informed methods [61] or closed-loop systems [62–64].

### 12. What do we know so far about the dose-response relationship?

Although a systematic review was not the primary objective of this study, we conducted a structured literature search to obtain an overview of previously published studies that explicitly investigated dose–response relationships in transcranial neuromodulation. Here, we summarize representative examples from this review to illustrate how

dose–response approaches have been implemented across modalities and dose dimensions. Full details of the search strategy, eligibility criteria, and data extraction procedures are provided in Supplementary Materials Sections S1–S3, along with the complete extracted dataset in the Supplementary Excel file.

### 13. Evidence from animal studies

In animal studies, clear but heterogeneous dose–response relationships have been observed across transcranial neuromodulation modalities and dose dimensions. Comprehensive details about previous dose–response evidence in animal studies can be found in Supplementary Materials S4. Briefly, in non-human primates, intensity- and spatially dependent neural and behavioral effects were demonstrated for cTBS and single-pulse TMS, with responses well described by sigmoidal dose–response functions and strong sensitivity to coil orientation and target distance [65,66]. In rodents, magnitude- and frequency-dependent neurovascular responses were identified following transcranial electrical stimulation, with detectable thresholds and partial saturation at higher field strengths [67,68]. Across transcranial focused ultrasound studies, dose-dependent modulation was observed across acoustic intensity and temporal parameters, including monotonic scaling of hemodynamic and neural responses, region- and state-dependent non-monotonic effects, and duration-dependent thresholds for functional activation [42–44,69,70]. In contrast, in electroconvulsive seizure models, threshold-type or inverted-U dose–response patterns were more commonly reported, in which behavioral or cellular effects emerged only above certain intensities or at moderate cumulative doses and then plateaued or diminished at higher doses [71–74]. See Supplementary Materials S4 for further details.

Animal models offer unique advantages for elucidating dose–response mechanisms in transcranial brain stimulation (e.g., tES), enabling simultaneous investigation of neuronal/molecular processes and behavioral outcomes [75,76]. However, anatomical, functional, and methodological differences between animal models and humans limit translational applicability. For instance, rodents (mice/rats) have smaller brains, requiring novel techniques to focalize stimulation, often diverging from human interventions [77,78]. Additionally, the absence of cortical gyri in rodents complicates replication of human brain dynamics [79]. Furthermore, stimulation electrodes in rodents are subdermal, with electric fields applied at a magnitude  $10 \times$  higher than human thresholds, hindering clinical translation [80,81]. Invasive rodent studies demonstrate that tES-induced electric fields (1.5–6 V/m) must exceed human/non-human primate thresholds (0.2–4.5 V/m) to modulate neuronal spiking [82–86]. This disparity could be attributed to differences in neuronal density, axon length and diameter [87,88], or the effects of anesthetics [89].

### 14. Evidence from human studies

#### 14.1. Evidence from magnitude-based dose manipulation

Across neuromodulation modalities, magnitude-based dose manipulation was the most commonly implemented dose dimension, but dose–response relationships were frequently non-linear, state-dependent, and outcome-specific rather than simple monotonic scaling. In TMS studies, increasing stimulation intensity often produced threshold effects, regime shifts (e.g., from inhibition to facilitation), or inverted-U profiles, with substantial inter-individual variability and spatial specificity across cortical networks, indicating that higher intensity did not uniformly yield larger or more beneficial effects [14,15,25,26,32,90–93]. Similarly, in tES studies, nominal current intensity was frequently associated with non-monotonic behavioral and physiological responses, with intermediate doses sometimes producing maximal effects and higher doses flattening or reversing responses [34,36,94–96]; modeling of electric fields further showed that received dose better

predicted outcomes than applied current in some paradigms [97–99]. In ECT, stimulus charge showed strong dose-dependent scaling of autonomic and neurochemical responses, yet this physiological scaling did not translate into proportional clinical improvement, highlighting dissociation between biological activation and therapeutic efficacy [48]. In contrast, available tFUS evidence demonstrated more monotonic magnitude–response relationships when acoustic pressure was corrected for skull transmission, emphasizing the critical role of biophysically accurate received dose in observing consistent dose–response effects [100,101]. Collectively, these findings suggest that magnitude alone is an insufficient predictor of outcome across neuromodulation modalities and that reliable dose–response characterization requires consideration of neural state, spatial targeting, and biophysical dose delivery in addition to nominal stimulus intensity. See Supplementary Materials S.5.1. for further details.

#### 14.2. Evidence from temporal pattern dose manipulation

Across modalities, temporal patterns emerged as a critical and independent dose dimension, with outcomes influenced not only by cumulative exposure but also by how stimulation was distributed over time. In TMS, increasing pulse counts [102,103], longer within-session exposure [104], and greater numbers of treatment sessions [105,106] were often associated with stronger physiological or clinical effects, consistent with dose accumulation, yet several studies demonstrated that altering delivery schedules (e.g., spacing or daily frequency) changed outcomes even when total pulse dose was held constant [107], indicating sensitivity to temporal distribution in addition to cumulative dose, with some protocols showing outcome-specific sensitivity to total pulse counts [108–110]. Similarly, tES studies showed both linear accumulation across repeated sessions [111] and non-linear or plateauing effects [112], with some paradigms exhibiting inverted-U relationships when dose was defined by the number of stimulation events aligned to specific brain states [113], emphasizing the importance of state-dependent timing rather than total stimulation time alone [114]. In ECT, treatment response was primarily related to the number of sessions and early-session efficiency [115], with patient sensitivity and baseline characteristics moderating temporal dose–response relationships, while stimulus magnitude was not systematically varied [115]. Collectively, these findings indicate that temporal pattern is not merely a proxy for cumulative dose but a distinct dose dimension that interacts with neural state, schedule, and individual responsiveness, often producing non-monotonic or outcome-specific dose–response profiles. See Supplementary Materials S.5.2. for further details.

#### 14.3. Evidence from spatial dose manipulation

Across modalities, spatial configuration strongly shaped effective dose and often determined whether magnitude-based dose–response relationships were detectable at all. In TMS, dose–response effects based on absolute intensity emerged only when stimulation was spatially aligned with functionally relevant targets, whereas threshold-normalized dosing or stimulation at standard locations frequently obscured dose–response patterns [16], indicating that targeting accuracy modulates sensitivity to dose escalation. In tES, changing electrode montage or return electrode placement substantially altered network engagement and regional physiological responses even when nominal current was held constant [116,117], demonstrating that field topology constitutes a primary dose dimension rather than a secondary modifier of intensity. Studies combining montage variation with E-field modeling showed that local received dose better predicted outcomes than applied current alone [35], and effects depend on polarity and targeted region [34,118]. Overall, spatial dose manipulation revealed that neuromodulation outcomes depend critically on how stimulation is distributed across brain networks, and that neglecting spatial configuration can lead to misleading conclusions about the presence or absence of

dose–response relationships. See Supplementary Materials S.5.3. for further details.

#### 14.4. Evidence from multi components dose manipulation

Studies that manipulated more than one dose component demonstrated that changes in stimulation outcomes could not be explained by any single parameter alone, and that both main effects and interactions between dose components were common. In TMS, corticospinal excitability increased with both intensity and pulse number, but significant interaction effects showed that additional pulses produced substantially larger MEP facilitation at higher intensities than at lower intensities [27], indicating that temporal summation depended on baseline stimulation strength rather than acting as a simple additive factor. In tES, studies that crossed intensity with session number, montage, polarity, or modeled electric field showed that behavioral and physiological effects were often driven primarily by temporal exposure (e.g., number of sessions) [112] or spatially localized E-field magnitude [35,37,114,118], while nominal current amplitude alone frequently failed to predict outcomes. For example, increasing session count produced clear improvements with plateauing after several sessions, whereas increasing current intensity or stimulation duration within typical ranges did not further enhance effects [112], and voxelwise E-field strength better predicted regional physiological changes than applied mA [35,37,114]. In tFUS, simultaneous manipulation of acoustic intensity, sonication duration, pulse repetition frequency, and duty cycle revealed distinct dose–response profiles for different parameters, with intensity and duration governing effect magnitude and persistence [101], while frequency showed a non-monotonic relationship with maximal facilitation at intermediate values [119]. Together, these studies demonstrate that neuromodulation dose operates in a multidimensional parameter space, where modifying one component can change the sensitivity to other components, and where outcome magnitude, duration, and spatial distribution may each depend on different combinations of stimulation parameters. See Supplementary Materials S.5.4. for further details.

Based on available evidence, the dose–response relationship in transcranial brain stimulation is highly complex and often deviates from a straightforward monotonic pattern. Across modalities—including tES, TMS, and tFUS—outcomes are influenced by diverse factors such as fluctuations in brain state, anatomical variability, and underlying neurophysiological mechanisms like calcium dynamics and synaptic plasticity. Concept of "no man's land" highlights a range of stimulation intensities where neither excitatory nor inhibitory effects dominate, potentially leading to minimal modulation of neural or behavioral outcomes. In this context, empirical bias arises when conclusions are drawn from a narrow set of stimulation parameters, increasing the risk that observed effects reflect local or idiosyncratic operating points rather than generalizable dose–response relationships. To mitigate this limitation, future studies should prioritize hypothesis-driven sampling of dose space, rather than exhaustive parameter permutation. Specifically, studies should aim to (i) probe a strategically expanded and better-resolved range of dose values within established safety and tolerability limits when mechanistically justified, (ii) manipulate key dose components selectively and a priori (e.g., magnitude or temporal structure, rather than all parameters simultaneously), (iii) quantify received dose using validated biophysical models or recordings to enable cross-study comparability, and (iv) incorporate multimodal outcome measures to distinguish true dose insensitivity from measurement-specific null effects.

### 15. Methodological considerations in measuring and reporting dose–response relationships

Robust characterization of dose–response relationships in transcranial brain stimulation requires transparent and standardized reporting of how dose is defined, modeled, and evaluated. At present, the

absence of unified reporting practices for received dose estimation, modeling assumptions, validation metrics, and analysis workflows substantially limits reproducibility and cross-study synthesis. Across the literature, stimulation dose is operationalized in markedly different ways, including binary contrasts, multi-level parameter sweeps, or continuous predictors, and may reflect delivered or modeled received dose. While such diversity is scientifically appropriate, key methodological details are often incompletely specified, including dose normalization procedures, spacing and ordering of dose levels, assumptions underlying statistical models, and criteria used to define meaningful dose–response effects. As a result, studies that appear methodologically similar may not be directly comparable or reproducible, and differences in reported outcomes may reflect undocumented analytical choices rather than biological variability [14,25,91]. This lack of standardized reporting has concrete methodological consequences. Inconsistent specification of dose sampling strategies and model assumptions impedes replication of individual studies and complicates interpretation of reported dose–response relationships. For example, studies variously apply logistic or sigmoidal fits to estimate thresholds or saturation effects [65,91], linear or quadratic regressions across dose levels [25,96], or mixed-effects models accounting for repeated measures and inter-individual variability [14,114], often without fully reporting model selection criteria, parameter constraints, or validation procedures. Without such information, it is difficult to assess whether observed dose–response patterns are robust, overfitted, or contingent on specific modeling choices. Additional challenges arise in temporal dose studies, where cumulative, block-wise, or session-based dose effects are analyzed using heterogeneous definitions of dose accumulation and persistence, frequently without standardized criteria for determining temporal integration or decay of effects [104,107,108]. Similarly, criteria for defining meaningful stimulation effects, including statistical thresholds, correction for multiple comparisons, responder classifications, and selection of primary endpoints, vary widely and are often insufficiently reported, limiting cross-study synthesis and meta-analytical integration [48,49]. Importantly, these limitations do not stem from analytical diversity per se, but from insufficient transparency and a lack of harmonized reporting standards. Addressing this gap underscores the need for consensus reporting guidelines to improve reproducibility and facilitate the rigorous synthesis of dose–response evidence. Ultimately, this methodological variability constrains the generalizability of findings, highlighting the critical need for standardized frameworks in study design and analysis. When establishing dose–response functions, careful attention must be given to the multi-faceted variables that influence both the dose and the response. These include parameters governing temporal and spatial precision (delivered dose; see Table 2) as well as the additional biophysical and physiological factors outlined below.

- 1. Brain state dependency:** Neural states—such as resting, task-based, or sleep states—significantly modulate responses to stimulation. For instance, TMS applied during rest can yield different outcomes compared to stimulation during a cognitive task. Even during the same cognitive task the level of difficulty of each trial can induce different outcomes and literally change dose–response results. While complete standardization of brain state across individuals and timepoints may not be feasible—given intrinsic variability in neural engagement—even when performing the same task or therapy, it remains essential to either monitor and model this variability (e.g., using concurrent EEG/fMRI, performance metrics, or latent state estimation) or control it to the extent possible through task design or timing of stimulation. Incorporating brain state as a dynamic and interacting factor will improve the interpretability and generalizability of dose–response findings.
- 2. Delivered dose range:** First, it should be recognized that dose is a multicomponent construct, and in dose–response studies any component of dose may be systematically varied to generate a dose–response curve. As defined in this review, dose includes

magnitude, temporal structure, and spatial configuration. Accordingly, dose–response curves can be obtained by varying any of these dimensions, or their combinations, although most existing studies have primarily focused on stimulus magnitude. For each dose component, meaningful characterization of dose–response relationships requires sampling across a range that is appropriate to the study's aims, rather than uniformly spanning the entire feasible parameter space. When the goal is to estimate the overall shape of a dose–response function, broader sampling across the safe operating range may be informative. However, hypothesis-driven designs that compare a limited number of theoretically or empirically motivated dose levels can also yield valid and interpretable insights, particularly when guided by prior evidence, safety considerations, or mechanistic predictions. Similarly, temporal parameters such as stimulation duration, frequency, or patterning may be varied selectively to probe specific response regimes, without requiring exhaustive exploration of all possible values. In this context, “dose–response” should be understood as the relationship between systematically manipulated dose components and observed outcomes within a defined and justified parameter range, rather than as a requirement to map the entire response curve. Importantly, each modality's safety constraints and prior knowledge should guide feasible parameter selection, while transparent reporting of which dose dimensions were varied—and why—remains essential for interpreting and comparing dose–response findings across studies.

3. **Received dose measurement:** The strength and orientation of the applied current—whether radial or tangential—significantly impacts neuronal polarization. Multi-scale modeling in electrical brain stimulation has demonstrated how the current direction influences excitability, particularly in pyramidal neurons. Integrating these models into dose–response studies improves precision in understanding brain stimulation effects.
4. **Off-target effects:** Peripheral stimulation, such as somatosensory or auditory activation, can confound dose–response interpretation. In TMS, realistic sham conditions should mimic the auditory and somatosensory effects of real stimulation without inducing cortical activation. Similarly, in tFUS, unintended mechanical or thermal changes may interfere with outcomes, necessitating precise control of acoustic parameters and skull attenuation measurements.
5. **Network-based effects:** Brain stimulation impacts both local and network-level regions. Functional connectivity analyses, such as TMS–fMRI, can reveal how stimulation spreads to remote areas, providing insights into dose-dependent activity changes across cortical and subcortical regions. This broader perspective is essential for understanding the therapeutic impact of stimulation.
6. **Population-specific considerations:** Variability in age, gender, and pathology significantly influences responses to stimulation. For instance, thinner skulls in children or certain populations may result in higher E-field intensities during tES. Accounting for such variability enhances the generalizability of findings.

Reporting considerations include consistency in reporting parameters, multi-modal approaches, accounting for individual variability, and reporting safety thresholds to enhance study reproducibility.

1. **Comprehensive reporting of dose:** All studies should provide a detailed account of stimulation parameters, including both delivered dose (Table 2) and received dose (e.g., computational head modeling to quantify E-field strength and directionality).
2. **Comprehensive reporting of response:** Selecting appropriate multi-modal approaches based on the research question enhances the accuracy of the spatial and temporal mapping of stimulation effects. For instance, TMS–EEG provides real-time measures of cortical excitability while fMRI reveals dose-dependent changes in functional connectivity. Additionally, detailed reporting of response parameters—from the device used to collect data to the methods

used for quantification—is essential for ensuring a clearer interpretation of results.

3. **Individual variability:** Reports should account for anatomical and physiological differences, such as skull thickness or age-related reductions in cortical plasticity, which can affect dose–response relationships. Including representative sample data or individualized measures (e.g., modeled E-fields) improves the precision of dose–response studies.
4. **Safety thresholds:** Explicit reporting of safety considerations is crucial for ensuring stimulation protocols remain within safe limits while achieving the desired neuromodulatory effects (e.g., cavitation thresholds in tFUS, auditory discomfort thresholds in TMS (sound levels generated by the rapid discharge of the magnetic coil during TMS), electrical dose calibration in ECT).
5. **Dose–response curve:** Clear documentation of how dose–response curves are explored—including parameter ranges and dosing intervals—is essential. Addressing ceiling effects or non-linear trends in dose–response relationships requires careful parameter selection and a well-defined methodology.
6. **Interpretation of dose–response relationships:** The interpretation of dose–response relationships should be carefully considered when reporting results, as it involves assessing how changes in stimulation parameters systematically affect physiological or behavioral outcomes. A clear example is TMS-evoked MEP, where an increase in stimulation intensity typically leads to larger MEP amplitudes, reflecting heightened corticospinal excitability. However, this relationship is not always linear—after reaching an optimal intensity, further increases may lead to response saturation or even paradoxical reductions due to inhibitory mechanisms. Similar non-linear or threshold-dependent effects are observed across other stimulation modalities, highlighting the importance of carefully mapping dose–response curves to ensure accurate interpretation and avoid misleading conclusions.

## 16. Conclusion

The dose–response relationship is central to understanding the mechanisms and optimizing the efficacy of transcranial brain stimulation. This review highlights the complexities of dose–response dynamics, spanning neural, physiological, behavioral, and non-neural levels. While foundational principles from pharmacology and animal studies provide a useful framework, transcranial brain stimulation for humans introduces unique challenges, including multidimensional dose parameters, response quantifications, individual variability, and intricate dose–response patterns. Advances in computational modeling, brain mapping tools (e.g., EEG, MEG, fMRI), behavioral/clinical assessments, and in-vivo recordings have shed light on these relationships but also underscore the need for further refinement in methodologies.

Despite significant progress, the field faces challenges in accurately defining and measuring both delivered and received doses. Variability in anatomy, ongoing brain states, and individual factors complicates the prediction of outcomes and necessitates a shift toward individualized stimulation models. Similarly, the observed non-linear and state-dependent dose–response patterns demand careful study design and comprehensive reporting of parameters. To bridge the gap between experimental findings and clinical applications, future research must integrate multi-modal approaches, validate computational models, and account for inter-individual differences. Standardized reporting of stimulation parameters and outcomes will be pivotal in advancing reproducibility and translational impact. Ultimately, improving our understanding of dose–response relationships will enhance the precision, safety, and therapeutic efficacy of transcranial brain stimulation, driving innovations in neuromodulation and brain health.

## CRedit authorship contribution statement

**Ghazaleh Soleimani:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Ivan Alekseichuk:** Writing – review & editing, Writing – original draft. **Christian Aurup:** Writing – review & editing, Writing – original draft. **Til Ole Bergmann:** Writing – review & editing, Writing – original draft. **Sven Bestmann:** Writing – review & editing, Writing – original draft. **Lysianne Beynel:** Writing – review & editing, Writing – original draft. **Carys Evans:** Writing – review & editing, Writing – original draft. **Flavio Frohlich:** Writing – review & editing, Writing – original draft. **Peyman Ghobadi-Azbari:** Writing – review & editing, Writing – original draft, Visualization. **Colleen A. Hanlon:** Writing – review & editing, Writing – original draft. **Florian Kasten:** Writing – review & editing, Writing – original draft. **Elisa E. Konofagou:** Writing – review & editing, Writing – original draft. **Maximilian Lueckel:** Writing – review & editing, Writing – original draft. **Javier Márquez-Ruiz:** Writing – review & editing, Writing – original draft. **Lucia Mencarelli:** Writing – review & editing, Writing – original draft. **Mohsen Mosayebi-Samani:** Writing – review & editing, Writing – original draft. **Cecilia Neige:** Writing – review & editing, Writing – original draft. **Alexander Opitz:** Writing – review & editing, Writing – original draft. **Angel V. Peterchev:** Writing – review & editing, Writing – original draft. **Oula Puonti:** Writing – review & editing, Writing – original draft. **Harold A. Sackeim:** Writing – review & editing, Writing – original draft. **Guillermo Sánchez-Garrido Campos:** Writing – review & editing, Writing – original draft. **Hartwig R. Siebner:** Writing – review & editing, Writing – original draft. **Axel Thielscher:** Writing – review & editing, Writing – original draft. **Andreas Vlachos:** Visualization. **Mihaly Voroslakos:** Writing – review & editing, Writing – original draft. **Michael A. Nitsche:** Writing – review & editing, Writing – original draft. **Sarah H. Lisanby:** Writing – review & editing, Writing – original draft. **Marom Bikson:** Writing – review & editing, Writing – original draft. **Hamed Ekhtiari:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Conceptualization.

## Declaration of competing interest

The City University of New York holds patents on brain stimulation with M.B. as inventor. M.B. has equity in Soterix Medical Inc. M.B. consults for, received grants from, assigned inventions to and/or serves on the Scientific Advisory Board of Boston Scientific, GlaxoSmithKline, Mecta and Halo Neuroscience. S.H.L. is an inventor on a patent on TMS coil design (no royalties). M.A.N. is on the Scientific Advisory Boards of Neuroelectrics and Precisis and has conducted consulting activities for Boehringer Ingelheim. H.R.S. has received honoraria as speaker and consultant from Lundbeck AS, Denmark, and as editor (Neuroimage Clinical) from Elsevier Publishers, Amsterdam, the Netherlands. He has received royalties as book editor from Springer Publishers, Stuttgart, Germany, Oxford University Press, Oxford, UK, and from Gyldendal Publishers, Copenhagen, Denmark. H.R.S. was supported by a grand solutions grant ‘Precision Brain-Circuit Therapy - Precision-BCT’ from Innovation Funds Denmark (grant no. 9068-00025B) and a collaborative project grant ‘ADaptive and Precise Targeting of cortex-basal ganglia circuits in Parkinson’s Disease - ADAPT-PD’ from Lundbeckfonden (grant no. R336-2020-1035). A.V.P. is an inventor on patents and patent applications on transcranial magnetic stimulation technology and has received patent royalties and consulting fees from Rogue Research; equity options, scientific advisory board membership, and consulting fees from Soterix Medical; equipment loans from Magventure; hardware donation from Magstim; and research funding from Motif. A.T. received support from the Lundbeck Foundation (grants R313-2019-622), the German Research Foundation (Research Unit 5429/1 (467143400, AT 1330/6-1, AT 1330/7-1) and the National Institute of Health (grant R01MH128422).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2026.103067>.

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