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Transcranial direct current stimulation: From mechanisms of action to practical recommendations

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Abstract

Over the past two decades, transcranial direct current stimulation has expanded substantially, both in basic research and in clinical applications. Despite this growth, the precise mechanisms by which brain stimulation modulates neural function remain only partially understood. This review integrates evidence suggesting that the effects of tDCS operate through three complementary mechanisms: (1) *transcranial mechanism* – involving polarity-specific modulation of cortical excitability and synaptic plasticity; (2) *peripheral mechanism* – in which stimulation of cranial and cutaneous nerves activates ascending neuromodulatory systems (noradrenergic, dopaminergic, and serotonergic); and (3) *neurovascular mechanism* – through which electric fields influence cerebral microcirculation and transiently alter the permeability of the blood–brain barrier. These mechanisms are likely to interact dynamically, shaping both the immediate and long-term behavioral and physiological effects of stimulation. Understanding their relative contributions is crucial for experimental design, electric field modeling, and interpretation of results. The translational potential of electrical brain stimulation is particularly promising as an adjunctive therapy in post-stroke rehabilitation, mood disorders, and targeted drug delivery. However, advancing the field will require systematic efforts to strengthen methodological rigor, optimize individualized dosing strategies, and refine mechanistically grounded protocols that ensure both reproducibility and clinical relevance.

Abbreviations:
attention deficit hyperactivity disorder (βADHD), blood-brain barrier (BBB), brain-derived neurotrophic factor (BDNF), dorsolateral prefrontal cortex (DLPFC), high-definition transcranial direct current stimulation (HT-tDCS), locus coeruleus (LC), locus coeruleus-noradrenergic system (LC-NE), magnetic resonance imaging (MRI), N-methyl-D-aspartate receptor (NMDA receptor), nitric oxide (NO), noradrenaline (NE), positron emission tomography (PET), salivary α-amylase (sAA), transcranial magnetic stimulation (TMS), tropomyosin receptor kinase B (TrkB), valine-to-methionine substitution at codon 66 (Val66Met)

Introduction

Brain stimulation is a central tool in contemporary neuroscience and clinical neurology, enabling targeted modulation of brain activity for both experimental and therapeutic purposes. Stimulation methods are broadly categorized as invasive or non-invasive (Bikson *et al.* 2016; Knotkova *et al.* 2019). Invasive stimulation methods, such as *deep brain stimulation, cortical surface stimulation, vagus nerve stimulation*, and *spinal cord stimulation*, deliver electrical currents via implanted electrodes to modulate neural activity within specific brain or peripheral circuits (Hariz, 2014; Kannan *et al.* 2025; Vetkas *et al.* 2025). In contrast, non-invasive brain stimulation encompasses techniques that modulate brain activity without surgical intervention, by delivering controlled electrical currents *(transcranial direct current stimulation)*, magnetic fields *(transcranial magnetic stimulation)*, or ultrasound *(focused ultrasound stimulation)* through the intact scalp and skull (Polanía *et al.* 2018). These externally applied physical fields influence neural function by altering neuronal membrane polarization, ion conductance, mechanosensitive elements, and neurovascular processes, thereby modulating neuronal excitability, synaptic plasticity, and information transmission (Lefaucheur *et al.* 2020; Nitsche & Paulus, 2000; Vasu & Kaphzan, 2022; Zhang *et al.* 2021).

Among non-invasive techniques, transcranial direct current stimulation (tDCS) has emerged as a prominent paradigm for modulating cortical excitability and investigating causal links between neural activity and behavior. Over the past two decades, its use has expanded nearly twentyfold (Web of Science data, 2025), reflecting its rapid integration into both cognitive neuroscience and clinical practice. Yet, despite this remarkable growth, the mechanisms through which electrical stimulation influences neural circuits and behavior remain incompletely understood – a critical challenge this selective review seeks to address.

As we discuss further below, tDCS can act directly on cortical circuits to modulate excitability, neuroplasticity, and network dynamics (i.e., *transcranial* mechanism), indirectly via peripheral nerves engaging ascending pathways (i.e., *peripheral* mechanism), as well as, more recently, through vascular effects (i.e., *neurovascular* mechanism) that influence cerebral blood flow and neurovascular coupling (Bahr-Hosseini & Bikson, 2021; Luckey *et al.* 2023; Nitsche & Paulus, 2000). Understanding how these distinct modes of action interact, and shape observed outcomes is critical for building comprehensive mechanistic models of neuromodulation, optimizing experimental design, and maximizing the translational potential of tDCS for basic research and clinical application.

Transcranial mechanisms: direct modulation of cortical excitability and network dynamics

tDCS enables non-invasive modulation of cortical activity through the application of weak, constant electrical currents (usually 1–2 mA for 20–40 minutes) to the scalp, primarily targeting cortical structures (Nitsche & Paulus, 2000; Polanía *et al.* 2011) but potentially influencing subcortical regions as well (Nonnekes *et al.* 2014). Rather than directly evoking action potentials, these fields induce subtle shifts in neuronal resting membrane potentials (Nitsche & Paulus, 2000) and modulate ongoing oscillatory activity (Keeser *et al.* 2011; Spitoni *et al.* 2013), thereby influencing excitability and synaptic plasticity within stimulated cortical regions or networks (Nitsche, Fricke, *et al.* 2003; Ranieri *et al.* 2012).

tDCS elicits both immediate (acute) and enduring (long-term) aftereffects, underpinned by distinct yet interacting neurophysiological processes that are critically dependent on current polarity. Acute effects emerge during stimulation and reflect immediate changes in membrane potential and neuronal excitability. Anodal stimulation typically increases cortical excitability through membrane depolarization, whereas cathodal stimulation decreases it via hyperpolarization (Liebetanz *et al.* 2002; Nitsche & Paulus, 2000, 2001). In cortical pyramidal neurons, anodal stimulation depolarizes the soma and basal dendrites while hyperpolarizing apical dendrites, whereas the reverse pattern occurs under cathodal stimulation (Aspart *et al.* 2018). Pharmacological studies have demonstrated that these acute shifts in excitability are partly mediated by voltage-gated sodium and calcium channels, which regulate transmembrane ion flux and influence neuronal responsiveness (Nitsche, Fricke, *et al.* 2003; Stagg & Nitsche, 2011). These polarity-specific effects modify spike threshold, firing probability, and dendritic integration of synaptic inputs, thereby shaping the input-output function and temporal dynamics of neural processing (Bikson *et al.* 2004; Stagg & Nitsche, 2011). Moreover, direct current exerts substantial effects on axon terminals, modifying sodium channel conductance, thereby polarizing the terminals and enhancing synaptic vesicle release (Vasu & Kaphzan, 2022). Computational studies further demonstrate that such polarizing effects on somata, dendrites, and axons critically depend on the orientation of these neuronal compartments relative to the field (Bikson *et al.* 2004), resulting in differential sensitivity to radial versus tangential cortical currents (Rahman *et al.* 2013). Together, these polarity-dependent cellular mechanisms account for the immediate and reversible changes in cortical responsiveness observed during stimulation, albeit with substantial interindividual variability driven by anatomical, physiological, and stimulation-related factors (Horvath *et al.* 2015; Li *et al.* 2015).

In contrast, aftereffects persist for minutes to hours following stimulation and are associated with changes in synaptic plasticity. These effects depend on NMDA receptor activation and calcium-dependent intracellular cascades, promoting long-term potentiation or depression of synaptic efficacy (Jamil & Nitsche, 2017; Roche *et al.* 2015). A critical mediator of these plastic changes is brain-derived neurotrophic factor (BDNF), which regulates synapse formation, dendritic spine density, and long-term synaptic modifications (Fritsch *et al.* 2010; Podda *et al.* 2016). Animal studies demonstrate that anodal tDCS increases BDNF secretion in stimulated cortical regions, and that pharmacological blockade of BDNF signaling (TrkB receptor antagonism) abolishes tDCS-induced motor learning enhancements, establishing a causal role for BDNF in tDCS aftereffects (Fritsch *et al.* 2010). In humans, genetic variation in the BDNF gene (Val66Met polymorphism; for more information see Notaras *et al.* 2015) modulates individual responsiveness to tDCS, with Met carriers showing attenuated plasticity and reduced behavioral benefits, highlighting the importance of BDNF-dependent mechanisms in clinically relevant outcomes (Cheeran *et al.* 2008; Fritsch *et al.* 2010). Pharmacological evidence reveals a hierarchical dependency between acute and plastic effects: sodium channel blockers eliminate both acute excitability changes and aftereffects, demonstrating that acute membrane polarization is a necessary prerequisite for inducing plasticity, whereas NMDA receptor antagonists abolish only aftereffects while sparing acute changes, indicating that acute polarization alone is insufficient without concurrent engagement of NMDA-BDNF-dependent plasticity pathways (Liebetanz *et al.* 2002; Nitsche, Fricke, *et al.* 2003). Such plastic changes lead to sustained alterations in functional connectivity within stimulated networks, providing a physiological substrate for the cognitive and clinical outcomes.

Numerous studies show that tDCS can modulate motor (Bastani & Jaberzadeh, 2012) and cognitive functions (Dedoncker *et al.* 2016; Lee *et al.* 2021) in healthy individuals. Systematic reviews suggest that stimulation of frontal regions, particularly the dorsolateral prefrontal cortex, can improve selective attention, working memory, and response inhibition, though effects are modest and depend on stimulation polarity, intensity, and individual baseline performance (Dedoncker *et al.* 2016; Hill *et al.* 2016; Simonsmeier *et al.* 2018). In the semantic domain, anodal stimulation of the left prefrontal cortex enhances inhibition of automatic associations, while cerebellar tDCS facilitates automatic semantic retrieval (Marko & Riečanský, 2021; Petríková *et al.* 2023). Overall, improvements in executive and control functions are more consistent when stimulation is task-coupled or repeated. Since executive functions are primarily mediated by the fronto-parietal control network, these findings suggest that tDCS enhances network efficiency within active task-relevant circuits rather than producing generalized increases in cortical excitability (Horvath *et al.* 2015; Mancuso *et al.* 2016; Westwood & Romani, 2017).

Moreover, tDCS has shown therapeutic potential across clinical populations, influencing behavioral, cognitive, and emotional domains. In neurological disorders, it has been associated with reduced seizure frequency (Sudbrack-Oliveira *et al.* 2021) and improved motor and language recovery after stroke, especially when combined with rehabilitation (Lefaucheur *et al.* 2017; Roche *et al.* 2015). In psychiatric conditions, meta-analyses report small-to-moderate antidepressant effects of prefrontal tDCS (Brunoni *et al.* 2016; Moffa *et al.* 2020) and preliminary benefits for schizophrenia and ADHD, though findings remain heterogeneous (Mondino *et al.* 2018; Westwood *et al.* 2022). Cognitive studies suggest enhanced memory consolidation and slow decline in mild cognitive impairment and early Alzheimer's disease (Hsu *et al.* 2015; Summers *et al.* 2016). In the behavioral domain, DLPFC stimulation has been linked to reduced craving and better impulse control in substance use disorders (Conti & Nakamura-Palacios, 2014). Overall, tDCS shows the greatest promise as an adjunctive therapy, enhancing pharmacological and behavioral interventions through modulation of cortico-subcortical networks such as the thalamus, amygdala, and striatum (Polanía *et al.* 2012).

Despite robust behavioral and clinical findings, modeling studies indicate that up to 75% of the applied current may not reach the cortex due to skull resistivity, and the portion that does produces weak intracortical fields (<1 V/m)—raising doubts about whether such mild polarization alone explains tDCS effects (Huang *et al.* 2017; Vöröslakos *et al.* 2018). This paradox has led to exploration of alternative mechanisms, particularly peripheral nerve activation. Boekholdt *et al.* (2021) demonstrated that transcranial currents can stimulate cutaneous and autonomic afferents, which in turn modulate cortical activity via ascending neuromodulatory systems. This bottom-up pathway, involving the reticular activating system, thalamic relays, and diffuse monoaminergic networks (noradrenergic, serotonergic, dopaminergic), may complement or in some cases substitute direct cortical polarization (Luckey *et al.* 2023; van Boekholdt *et al.* 2021). Such insights broaden the theoretical framework of electrical brain stimulation and link tDCS to peripheral neuromodulation paradigms.

Peripheral mechanisms: indirect modulation via transcutaneous pathways

In standard tDCS protocols, the applied current must traverse the scalp, skull, and cerebrospinal fluid before reaching the cortical surface, where it is attenuated

to electric field strengths of typically less than 1 V/m. However, because the electrodes are placed directly on the skin, peripheral nerves are exposed to substantially higher fields (up to > 20 V/m) raising the possibility that some of tDCS's effects may arise through peripheral rather than purely transcranial mechanisms (Asamoah *et al.* 2019; Rampersad *et al.* 2014).

Evidence from transcutaneous electrical nerve stimulation supports this view: although originally developed for the treatment of neuropathic disorders and pain through direct peripheral nerve activation (De Ridder & Vanneste, 2017), recent findings demonstrate that peripheral stimulation can also influence central nervous system activity and cognitive processes (Byczynski *et al.* 2025; Luckey *et al.* 2023; Vanneste *et al.* 2020). According to the *transcutaneous pathway hypothesis*, activation of peripheral nerves (such as the occipital, trigeminal, or vagus nerve) can modulate central neuromodulatory systems via projections to the nucleus tractus solitarius (NTS; Luckey *et al.* 2023). One line of evidence supporting this hypothesis comes from studies of greater occipital nerve stimulation, which has been shown to influence locus coeruleus (LC) activity through the NTS (Vanneste *et al.* 2020). The LC serves as the brain's principal source of noradrenaline (NE), forming the LC–NE system, which critically modulates cortical excitability, enhances signal-to-noise ratio, and facilitates synaptic plasticity (Sara, 2009; Schwarz & Luo, 2015) – i.e., the very neurophysiological functions typically attributed to the transcranial effects of tDCS. Through these neuromodulatory effects, the LC–NE system plays a crucial role in regulating arousal, attention, and memory (Robison *et al.* 2018; Unsworth *et al.* 2018; Unsworth & Robison, 2017).

To address this peripheral pathway systematically, Vanneste and colleagues (2020) investigated the effects of tDCS on LC activity, using indirect physiological markers such as pupillary dynamics (pupillometry), salivary α-amylase (sAA) levels, and event-related potentials (P3b amplitude). The study demonstrated that active tDCS targeting greater occipital nerves produced significant increases in all three LC-associated markers, accompanied by improvements in long-term memory performance, whereas this cognitive effect could not be completely explained by the transcranial pathway itself. Importantly, peripheral stimulation may engage a broader network of neuromodulatory nuclei, including the nucleus basalis (cholinergic system), the raphe nuclei (serotonergic system), as well as the substantia nigra and ventral tegmental area (dopaminergic system; Collins *et al.* 2021; Majdi *et al.* 2024; Tyler *et al.* 2015) each exerting distinct influences on arousal, affect/emotion, motivation, and cognition, systems that are commonly dysregulated in neuropsychiatric individuals.

Finally, it should be noted that the peripheral pathway hypothesis remains a relatively new proposal and requires further empirical validation and replication. For example, the study by Vanneste *et al.* (2020) was based on a relatively small sample (n < 30), and its findings have yet to be reproduced by other groups. Moreover, the precise mechanisms (e.g., neuromodulatory systems and cortical networks) through which peripheral nerve stimulation influences complex cognitive and affective processes are not yet fully understood and warrant deeper mechanistic investigation. Nonetheless, the transcutaneous pathway represents a theoretically grounded mode of tDCS action, one that should be carefully considered when designing and interpreting studies that assume a purely transcranial mechanism.

Neurovascular mechanisms: indirect modulation via neurovascular interactions

The effects of electrical currents on the vascular system have been investigated for decades, with early studies demonstrating modulation of vascular tone and blood flow (Cancel *et al.* 2018; Lopez-Quintero *et al.* 2010). Nevertheless, these vascular phenomena were largely overlooked in brain stimulation research until recently. The broad spectrum of physiological, cognitive, and affective outcomes reported following tDCS suggests that its mechanisms of action extend beyond purely neuronal and synaptic modulation. Consistent with this view, emerging evidence indicates that, in addition to transcranial and peripheral effects, tDCS can directly influence cerebral vasculature and blood–brain barrier (BBB) dynamics (Bahr-Hosseini & Bikson, 2021; Shin *et al.* 2020; Xia *et al.* 2021). Specifically, tDCS has been shown to modulate cerebral microcirculation and transiently increase BBB permeability, supporting a broader neuromodulatory framework that integrates neurovascular alongside classical neurophysiological mechanisms.

Shin *et al.* (2020) demonstrated that anodal tDCS (up to 1 mA for 20 minutes) can transiently enhance BBB permeability in a dose-dependent manner. Notably, this effect was more pronounced for large solutes than for small molecules, indicating selective modulation of BBB transport pathways. Mechanistically, this process appears to be mediated by electro-osmotic fluid movement and activation of endothelial nitric oxide synthase, resulting in elevated nitric oxide (NO) production critical vasodilator and regulator of vascular tone. Increased NO levels induce short-lasting vasodilation and a temporary reduction in transendothelial electrical resistance, thereby facilitating solute passage across the BBB, particularly for larger molecules. Complementing these findings, Xia *et al.* (2021) reported that tDCS alters solute diffusivity within brain tissue, increasing the effective diffusion coefficient by approximately 10% for small solutes and up to 120% for large solutes, with values returning to baseline within 25–30 minutes post-stimulation. Moreover, tDCS transiently expands the

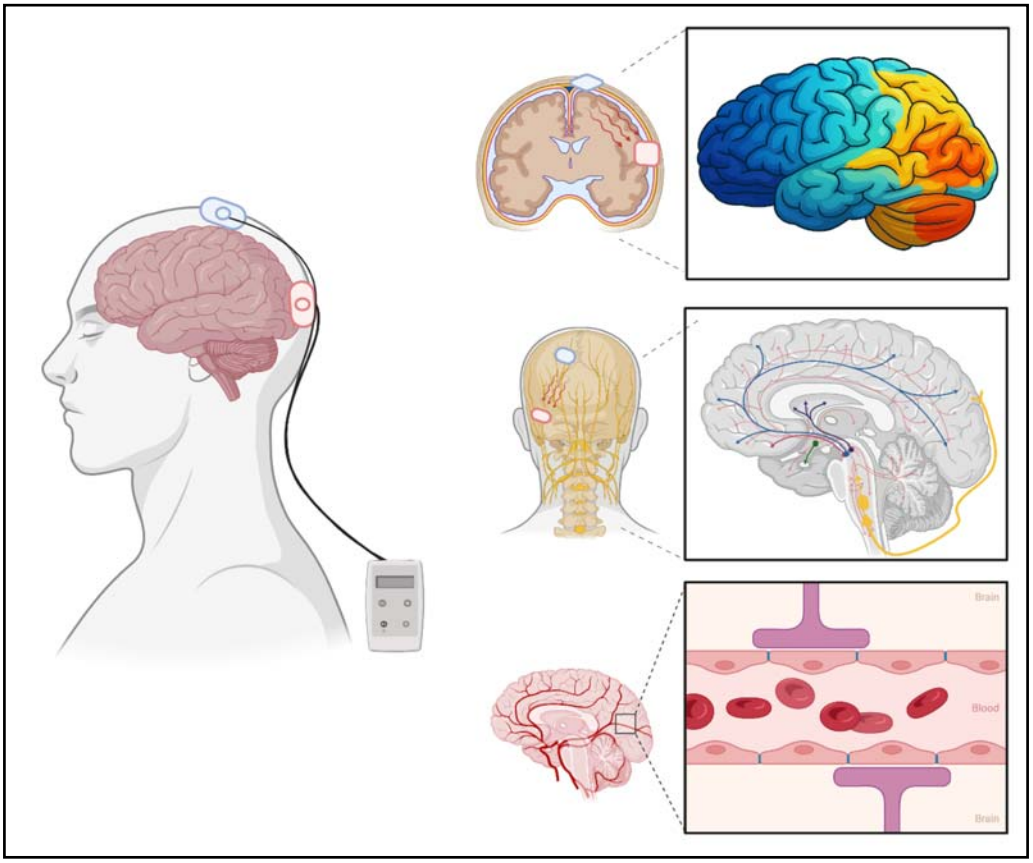

Fig. 1. Three Interacting Mechanisms of tDCS: Transcranial, Peripheral, and Neurovascular
Note: The schematic illustrates the three principal mechanisms of transcranial direct current stimulation (tDCS): (i) transcranial modulation of cortical and subcortical regions, (ii) transcutaneous activation of peripheral afferents, and (iii) neurovascular modulation of cerebral microcirculation and blood–brain barrier permeability. (Created in BioRender. Kubinec, A. (2025) https://BioRender.com/hbasqdv)

extracellular space by approximately 1.5-fold, thereby facilitating molecular transport and diffusion within neural tissue.

Collectively, these observations support *the neurovascular hypothesis*, which proposes that tDCS can transiently modulate BBB properties and endothelial function, influencing molecular transport and neurovascular signaling. Such modulation may help explain some of the heterogeneous behavioral, cognitive, and emotional effects observed following tDCS, as temporary alterations in BBB permeability could affect the brain microenvironment, neuroinflammatory responses, and the bioavailability of neuroactive compounds (Mielke *et al.* 2013; Stagg *et al.* 2013). However, it is important to note that most evidence for these neurovascular effects derives from animal studies, and their translational validity in humans remains uncertain (Jackson *et al.* 2016). Therefore, the clinical relevance of these mechanisms warrants further investigation through rigorously controlled human studies combining neuroimaging with physiological markers of cerebral perfusion and BBB integrity.

From Mechanisms to Applications

The preceding sections outlined three complementary mechanisms through which tDCS can modulate brain function. Understanding these mechanisms provides a foundation for transforming physiological and physical insights into methodological recommendations and therapeutic optimization.

Heterogeneity and Dosing

A major obstacle for both experimental reproducibility and clinical translation is the pronounced inter-individual variability in behavioral and physiological responses (Horvath *et al.* 2015; Li *et al.* 2015; López-Alonso *et al.* 2014; Wiethoff *et al.* 2014). This variability necessitates systematic control of both biological and contextual variables.

Reducing such variability requires consideration of pre-stimulation conditions, sleep, caffeine intake, medication, and the mood to minimize uncontrolled variance (Bradley *et al.* 2022; Polanía *et al.* 2011). Measuring and statistically accounting for baseline excitability, connectivity, or oscillatory dynamics allows for state-dependent modeling of responses to tDCS (Bradley *et al.* 2022). On anatomical level, individual current-flow modeling software (e.g., SimNIBS, ROAST) can guide montage selection and predict induced field strength (Huang *et al.* 2017; Laakso *et al.* 2015; Opitz *et al.* 2015; Thielscher *et al.* 2015), hence providing better overview of the relative strength and spatial distribution of polarizing current induced by tDCS. Although these simulations simplify tissue conductivity and cannot capture ongoing physiological fluctuations (Huang *et al.* 2017), they represent an essential step toward montage selection and individualized dosing.

Unlike pharmacological interventions, tDCS lacks a unified dosing metric that integrates current intensity, duration, electrode configuration, and anatomy. Current density alone poorly predicts neural engagement because this relationship depends on stimulation polarity, relative orientation of the targeted cortical layers, and network-level dynamics. Model-based metrics that estimate local electric-field magnitude and direction in target regions, or compute the volume of activated tissue, could enable more reproducible dose–response characterization (Esmaeilpour *et al.* 2020; Woods *et al.* 2016). Combining such modeling with within-subject or crossover designs can further reduce interindividual variance and strengthen causal inference. Interestingly, the effects of tDCS may differ between healthy and clinical populations, which is consistent with homeostatic plasticity principles: while healthy brains near their functional ceiling show limited room for enhancement, pathological networks may normalize toward baseline, thus tDCS effects are normalizing rather than enhancing (Krause & Kadosh, 2014; Silvanto & Pascual-Leone, 2008). However, clinical studies also demonstrate substantial variability in treatment response (Sarkis *et al.* 2014), suggesting that individual differences in baseline brain state, pathology severity, and other factors contribute to outcome heterogeneity.

Overall, reducing tDCS variability requires systematic control of pre-stimulation factors (sleep, caffeine, medication, mood), measurement of baseline brain state (excitability, connectivity, oscillatory dynamics), and individual current-flow modeling to predict electric-field distribution. Developing unified dosing metrics that integrate current intensity, duration, electrode configuration, and individual anatomy will be essential for achieving replicable and clinically meaningful neuromodulation.

Addressing Complex Mechanisms

A fundamental challenge in tDCS research is achieving sufficient spatial precision to modulate targeted neural circuits without affecting neighboring regions. Anatomical specificity, the ability to confine current flow to specific brain structures is inherently limited in conventional tDCS due to diffuse transcranial current spread. Large electrode configurations (typically 25-35 cm^2) produce broad electric fields that simultaneously affect multiple cortical regions and their interconnected networks, with substantial current reaching adjacent and even contralateral structures (Bikson *et al.* 2004; Huang *et al.* 2017; Rahman *et al.* 2013). To address this limitation, high-definition tDCS (HD-tDCS) employs smaller electrodes (typically 1-2 cm diameter) arranged in specific spatial configurations—most commonly a 4×1 ring montage, where a central electrode is surrounded by four return electrodes—to concentrate current flow in more focal cortical regions (Datta *et al.* 2009; Kuo *et al.* 2013). Computational modeling indicates that HD-tDCS can achieve comparable peak current densities to conventional tDCS while reducing the stimulated cortical volume by up to 50%, thereby enhancing spatial targeting and reducing off-target effects (Datta *et al.* 2009; Edwards *et al.* 2013). However, HD-tDCS presents practical trade-offs: increased setup complexity and duration, higher sensitivity to electrode positioning errors, potentially reduced tolerability due to elevated current density at electrode sites, and higher equipment costs (Alam *et al.* 2016; Kuo *et al.* 2013). Moreover, even with optimized HD-tDCS configurations, the induced electric fields remain relatively diffuse compared to focal neuromodulation techniques such as transcranial magnetic stimulation, highlighting the continued importance of complementary strategies for achieving anatomical specificity (Woods *et al.* 2016).

Functional specificity, the ability to selectively modulate only those neural networks that are currently active (Bikson & Rahman, 2013)— can be achieved by coupling acute stimulation with an ongoing task that engages the relevant pathways, thereby aligning externally induced polarization with endogenous neural activity. This strategy has been shown to enhance both the magnitude and reproducibility of stimulation effects relative to offline protocols (Gill *et al.* 2015; Mancuso *et al.* 2016). For offline applications, repeated or spaced tDCS sessions can induce cumulative and long-lasting plastic changes with potential to support rehabilitation after stroke, cognitive enhancement, or mood stabilization (Fregni & Pascual-Leone, 2007; Lefaucheur *et al.* 2017; Reis *et al.* 2009). Similarly, optimal results are obtained when stimulation is paired with learning or training paradigms, reinforcing plasticity within relevant neural networks (Nitsche, Schauenburg, *et al.* 2003).

To disentangle transcranial from peripheral contributions to tDCS effects, studies should employ active control conditions that match peripheral nerve stimulation yet diverge in cortical targeting. If comparable effects occur in peripheral nerves, any physiological or behavioral outcomes of tDCS can thus be attributed to transcranial mechanisms. Alternatively, topical anesthetics such as lidocaine/prilocaine gel can be applied under the electrodes to suppress peripheral input while preserving cortical current flow, improving blinding and interpretability of the tDCS effects (Vanneste *et al.* 2020).

Furthermore, physiological indices such as pupil diameter, sAA, or spontaneous blink rate (a proxy for dopaminergic activity; Jongkees & Colzato, 2016), or other indices of autonomic nervous system activity (e.g. skin conductance, heart rate variability) offer tools to assess whether tDCS engages peripheral and neuromodulatory pathways. Incorporating these measures as covariates or mediators in statistical analyses enables statistical control and/or decomposition of these parallel mechanisms of action. Pharmacological manipulations further deepen this approach

by enabling a systematic and causal manipulation of the putative systems: blockade of dopaminergic D_2 receptors, for instance, abolishes anodal tDCS-induced plasticity in the motor cortex (Nitsche *et al.* 2006), confirming a causal dopaminergic role and suggesting that combined tDCS–pharmacotherapy may enhance or verify mechanistic pathways. Conversely, when the goal is to study or implement peripheral neuromodulation per se, montage and electrode spacing can be optimized to maximize superficial current flow and minimize cortical penetration, effectively isolating peripheral pathways.

Regarding the neurovascular mechanisms, controlled, short-lived increases in BBB permeability could facilitate the delivery of large or hydrophilic molecules that normally fail to cross the barrier (Lipsman *et al.* 2018). This principle may be particularly valuable in Alzheimer's disease, where transient BBB modulation could enhance penetration of monoclonal antibodies against amyloid or tau aggregates and accelerate their clearance (de Koning *et al.* 2025). In neuro-oncology, montage-guided tDCS could increase intratumoral concentrations of chemotherapeutic agents such as temozolomide while limiting systemic exposure (Shin *et al.* 2020). Similarly, in pharmacoresistant epilepsy or ischemic stroke, tDCS-induced vascular modulation may improve local drug bioavailability or cerebral perfusion (Bahr-Hosseini *et al.* 2023).

These possibilities must, however, be balanced against safety concerns. Excessive or prolonged BBB opening could allow entry of neurotoxic plasma proteins or inflammatory mediators (Jackson *et al.* 2016). Determining safe, reversible, and spatially controlled stimulation parameters is therefore essential. Future translational studies should integrate high-resolution neuroimaging (dynamic MRI, arterial spin labeling, PET) with pharmacokinetic assays to map the spatial and temporal dynamics of BBB modulation in humans.

Conclusion

This selective review has synthesized evidence that tDCS operates through three complementary pathways such as transcranial modulation of cortical excitability, peripheral activation of ascending neuromodulatory systems, and neurovascular interactions affecting cerebral microcirculation and BBB permeability, each contributing distinct yet interconnected mechanisms that shape its physiological and behavioral outcomes. Moving forward, protocol optimization requires integration of individualized electric-field modeling, task-coupled protocols, active control conditions that dissociate transcranial from peripheral mechanisms using autonomic indices and neuroimaging biomarkers, and systematic assessment of neurovascular effects. Translational applications, particularly adjunctive use in stroke rehabilitation, mood disorders, and potentially targeted drug delivery, show promise but demand rigorously controlled trials with adequate sample sizes, preregistration, and systematic replication to establish reproducible dose–response relationships. Ultimately, advancing tDCS from an experimental tool to a clinically validated intervention will require interdisciplinary collaboration bridging neuroscience, engineering, and clinical medicine to develop mechanistically informed, individually optimized, and empirically robust neuromodulation strategies.

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Declaration of interests

The authors have no relevant financial or non-financial interests to disclose.

Data availability statement

This study has no associated data.

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