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From cranium to brain: Rethinking tES neuromodulation through the peripheral pathways

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ABSTRACT

Transcranial electrical stimulation (tES) is traditionally framed as a purely cortical intervention, and weak direct or alternating currents delivered through scalp electrodes are assumed to modulate excitability or entrain oscillations directly under electrodes. However, a growing body of evidence suggests that this transcranial view is incomplete. We synthesized converging human and animal evidence showing that tES also co-stimulates cranial and cervical nerves, especially branches of the trigeminal and greater occipital nerves, which engage deep brainstem neuromodulatory nuclei, such as the locus coeruleus and raphe. Activation of these transcutaneous pathways can mediate many behavioral and physiological effects attributed to direct cortical polarization. We propose an integrated dual-route framework in which tES outcomes reflect the weighted sum of (i) local electric field effects on the cortex, and (ii) brainstem neuromodulation initiated transcutaneously. This model explains spatial-specificity paradoxes, low-intensity effects, and sham inconsistencies and mandates revised control conditions that mask both routes. Recognizing the transcutaneous contribution not only explains the mixed findings but also introduces new opportunities that can ultimately improve therapeutic efficacy.

1. Introduction

Transcranial electrical stimulation (tES) is a non-invasive method of stimulating the brain, encompassing various modalities such as transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) [1]. Despite its popularity, the exact mechanisms through which tES changes neuronal activity and shapes neural circuits remain largely unknown [2].

For many years, the dominant theory of tES has emphasized the direct effects of electrical stimulation on cortical neurons, a process hereafter referred to as the transcranial mechanism [1,3,4]. An electric field produced inside the skull by low-amplitude current flowing between scalp electrodes can change the membrane potential of cortical neurons (tDCS) or entrain endogenous neural oscillations to the frequency of the applied current, synchronizing the timing of neuronal firing with the stimulation waveform (tACS) [1,5,6]. This perspective holds that changes in cognitive or behavioral functions are caused by this induced shift in neuronal excitability or neuronal entrainment [7–10]. In this framework, tES is considered a "cortical stimulator." Based on the assumption that the applied electrical current exerts non-uniform effects across cortical circuits—with relatively stronger modulation in regions located beneath and between the electrodes—researchers have targeted specific brain areas, such as the motor cortex for neurorehabilitation and the dorsolateral prefrontal cortex (DLPFC) for the modulation of working memory [11,12]. According to current-flow models, the brain's electric field under tDCS is weak (about 0.2–0.5 V/m in cortical tissue) but strong enough to modulate neuronal membrane potentials over minutes, thereby priming neural plasticity or network dynamics, even at conventional intensities (1–5 mA) [13,14]. It has been implicitly assumed that these direct in-brain electric fields cause the observed cognitive or therapeutic effects of tES [13,14].

The current model has several important limitations, despite successfully guiding research in the field. Whether the weak electric fields generated by tES can reliably produce reported changes in cognition and behavior remains a subject of scientific debate [15–17]. Additionally, some tES effects, particularly in cognitive studies, have shown variability across tasks, protocols, and laboratories [18–20]. These

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differences indicate that tES outcomes are likely influenced by multiple factors, including montage, stimulation dose, individual anatomy, brain state, task demands, outcome measures, and possibly peripheral co-activation [21].

A growing body of evidence shows that the traditional explanation—direct modulation of cortical tissue beneath the electrode—might not suffice to explain all changes observed following tES. Earlier work had raised the possibility that indirect effects of tES, including peripheral stimulation, should be more carefully investigated in experimental designs [22,23]. Building on this line of thought, recent studies have provided converging evidence from both human and animal studies, further supporting the involvement of peripheral pathways [13,24–26]. In particular, researchers are beginning to "look outside the cranium" to explain how tES causes cognitive and behavioral changes [27,28]. Importantly, although we use tES here as an umbrella term encompassing modalities such as tDCS, tACS, and tRNS, the empirical evidence reviewed in this article is currently strongest for tDCS, with additional but more selective support from tACS studies, whereas the relevance to tRNS remains less well established. The next section examines limitations of the transcranial paradigm and presents evidence supporting peripheral mechanisms of action in tES neuromodulation (hereafter referred to as the transcutaneous mechanism).

2. Cracks in the paradigm: challenging the transcranial mechanism

The idea that tES acts only through direct cortical modulation has been increasingly complemented by studies examining additional pathways [25–27]. Importantly, tES can stimulate peripheral excitable elements along its current path, in addition to brain tissue [23,29,30]. This does not imply that peripheral pathways explain all variable or inconsistent tES findings, but it does indicate that they should be considered when interpreting stimulation effects. To further understand the source of tES-induced cutaneous sensations, we now discuss evidence that DC can activate skin afferents not only through the applied current itself, but also through electrochemical products generated at the electrode–skin interface. Martinsen et al. [31] showed that perception of cutaneous DC depends on total current and spatial summation rather than current density alone, and that sensations may persist after current offset, suggesting a contribution from current-induced chemical products [31]. This is important for tDCS because commonly reported sensations such as tingling, itching, warmth, burning, or pinching may reflect activation of different cutaneous afferents through both electrical and electrochemical mechanisms [30,32,33]. Thus, peripheral activation during tES is influenced by waveform, intensity, electrode area, polarity, electrolyte composition, and montage, and should be taken into account when assessing physiological effects as well as sham blindness [34,35]. Hence, these peripheral pathways may confuse or even overpower the intended direct cortical effects if they have downstream neural effects [2]. Several lines of evidence have raised concerns that the transcranial model is insufficient to fully account for observed phenomena.

- *Spatial Specificity and shared peripheral pathways:* tES montages intended to target different cortical regions may occasionally produce comparable behavioral or physiological effects. This does not by itself prove peripheral nerve involvement, because similar outcomes may also reflect distributed cortical current flow, network-level effects, task dependence, or inter-individual variability [36,37]. Nevertheless, such findings make a strictly local cortical interpretation less straightforward and raise the possibility that different montages may partly recruit shared peripheral pathways, such as trigeminal branches over the frontal and temporal scalp [38,39]. This possibility should be tested directly using route-specific controls, including bipolar skin/peripheral nerve-targeting montages, peripheral nerve block conditions, or transcutaneous-only stimulation.
- *Residual Effects in Sham:* Participants still experience initial tingling under "sham" tES conditions, in which the current is momentarily increased and then turned off to simulate sensation [40,41]. Accordingly, sham does not fully eliminate peripheral nerve activation, but rather shortens its duration. Although the brief exposure used in the sham is unlikely to reproduce the full neuromodulatory consequences of sustained active stimulation, it may not be entirely physiologically inert. As discussed later in this review, activation of trigeminal and related peripheral pathways can recruit brainstem neuromodulatory nuclei such as the locus coeruleus and dorsal raphe, producing downstream effects on cortical and hippocampal activity [24,26,27]. In animal studies, peripheral nerve stimulation has been shown to induce prolonged changes in brainstem firing and, in some paradigms, brief post-learning peripheral stimulation was sufficient to enhance later memory performance [27]. Thus, transient peripheral co-activation during sham may partially reduce the contrast between sham and active conditions, complicating interpretation.
- *Low-Intensity Effects:* Some studies have found physiological or cognitive effects at tES intensities so low that the intracranial electric field can be considered negligible. For instance, currents ≤ 1 mA or montages that probably produce little cortical current have been shown to improve mood or attention [42,43]. Given that transcranial stimulation at these amplitudes is unlikely to directly evoke local cortical action potentials, it may instead modulate ongoing neuronal activity through subthreshold membrane polarization [13]. Such results should be interpreted within a dual-route framework rather than taken as evidence for one mechanism alone.

Together, these observations suggest that tES effects may reflect both cortical electric-field effects and peripheral co-activation, with the relative contribution depending on modality, montage, and stimulation intensity. The relative weighting of these routes is likely modality-specific. In tDCS, polarity-dependent cortical excitability changes may coexist with peripheral neuromodulatory influences [25,44]; in tACS, rhythmic peripheral recruitment may interact with cortical entrainment [13]; and in tRNS, the extent of peripheral contribution remains to be determined. Recognizing this dual mechanism is crucial, as it affects how experiments are designed and how results from previous studies are interpreted. If peripheral pathways are involved in how tES affects the brain, which pathways are involved, and how do they function? To answer this, we focus on the often-neglected trigeminal and greater occipital nerves (GON) and review emerging data that support their role in neuromodulation.

3. Peripheral pathways to the brain: the neglected routes

A growing body of evidence suggests that tES may inadvertently stimulate the cranial/peripheral nerves, offering an additional neuromodulation pathway [13,24,25,27]. These transcutaneous pathways include the GON [27] and branches of the trigeminal nerve on the face and scalp (Fig. 1) [13].

4. Trigeminal nerve: A gateway from skin to brainstem

The forehead, scalp, and face receive sensory innervation from the ophthalmic and maxillary branches of the trigeminal nerves. Importantly, these are the exact areas where tES electrodes are frequently positioned (Fig. 1) [45]. It has been shown that, in addition to generating an electric field in the cortex, tES also generates a stronger electric field in the scalp, which stimulates peripheral nerves [13,22]. tES activation of the trigeminal nerve and its afferent fibers sends signals to the trigeminal nuclei in the brainstem (the principal sensory nucleus, spinal trigeminal nucleus, and mesencephalic nucleus of the trigeminal nerve)

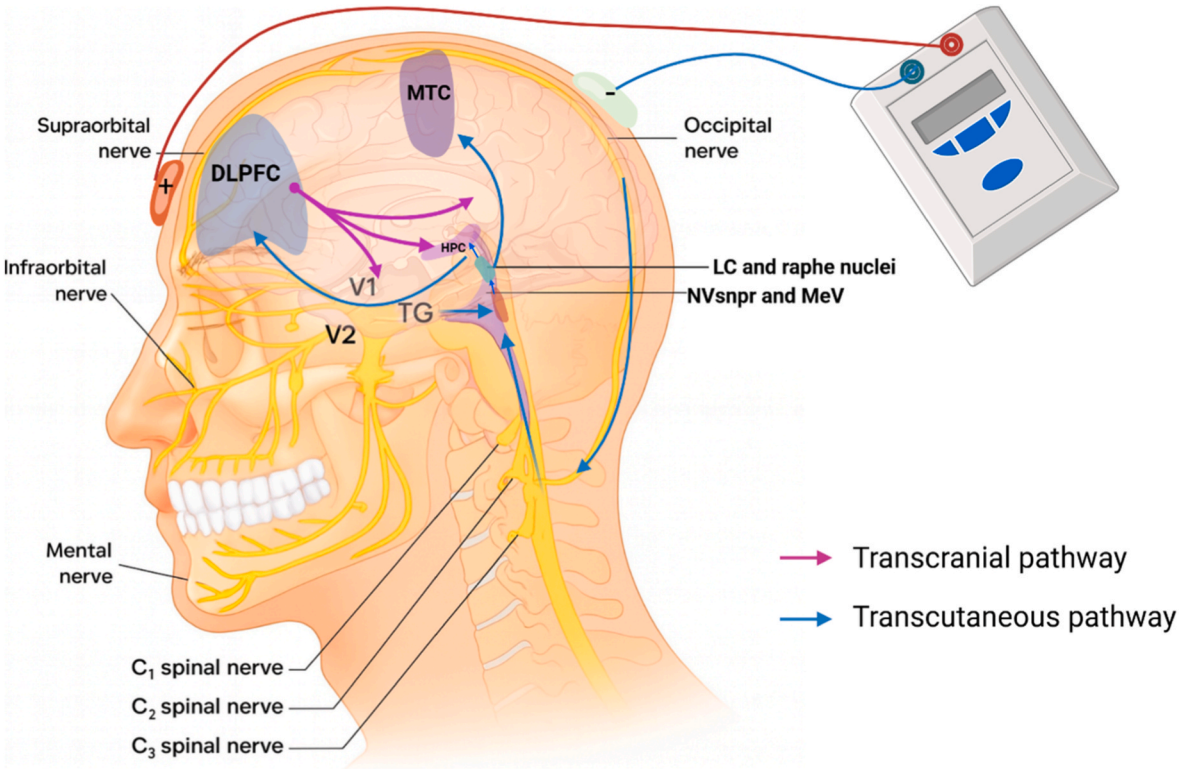

Fig. 1. Proposed peripheral pathways for trigeminal nerve–induced neuromodulation. This schematic illustrates how transcranial electrical stimulation (tES) may indirectly influence brain function through peripheral cranial nerves, particularly the branches of the trigeminal nerve. Electrical current applied via scalp electrodes (+, –) can activate superficial branches of the trigeminal nerve (V1, V2, infraorbital, supraorbital, and mental nerves), which project to sensory brainstem nuclei, including the trigeminal principal sensory nucleus (NVsnpr) and mesencephalic trigeminal nucleus (MeV). These brainstem relays connect to the locus coeruleus (LC) and raphe nuclei, major neuromodulatory centers that release norepinephrine and serotonin, respectively. Ascending projections from these nuclei (blue, transcutaneous pathways; purple, transcranial pathways) influence widespread cortical and subcortical regions such as the hippocampus (HPC), motor cortex (MTC), and dorsolateral prefrontal cortex (DLPFC). This model challenges the traditional view that tES effects are exclusively transcranial, highlighting instead that activation of peripheral nerves—including trigeminal and cervical spinal afferents (C1–C3)—can engage central neuromodulatory circuits and thereby modulate cognition, mood, and behavior.

[25,46]. These brainstem nuclei connect to the locus coeruleus (LC), a pons nucleus that widely releases norepinephrine (noradrenaline) throughout the brain [24]. It has been demonstrated that trigeminal nerve stimulation increases the brain's LC activity [24] and norepinephrine release [29,47]. This is noteworthy because cortical excitability, synaptic plasticity, and cognitive functions, such as memory, arousal, and attention, are all strongly modulated by the LC-noradrenergic (LC-NE) system [48]. The release of norepinephrine from an activated LC can improve learning and memory formation by enhancing glutamate-dependent plasticity and long-term potentiation (LTP) in cortical circuits [49–51]. By acting on β-adrenergic receptors, norepinephrine lowers the threshold for LTP induction through a mechanism called metaplasticity, which initiates signaling cascades. The synaptic strength and plasticity necessary for memory consolidation are improved by this modulation [49]. Norepinephrine can also increase general cortical excitability and cognitive flexibility [52]. Accordingly, if tES enhances working memory or attention, it might be partially due to LC-driven neuromodulation, which raises the signal-to-noise ratio in cortical networks (gain modulation), as opposed to (or in addition to) directly depolarizing cortical neurons [53]. One would anticipate downstream effects on memory-related areas (such as the hippocampus) through increased noradrenaline signaling in active tES conditions that stimulate the trigeminal nerve (Fig. 1) [2]. However, such neuromodulatory cascades do not occur in true sham conditions with no peripheral activation, which could theoretically lead to different cognitive outcomes [28].

The trigeminal pathway theory is supported by research in both humans [23,27] and animals [17,21]. Direct stimulation of trigeminal nerve fibers (TN-DCS) has been shown to increase activity in the LC and other brainstem nuclei in animal models [21], resulting in heightened arousal and neuroplastic alterations [47,53]. For instance, applying tDCS-like currents to the trigeminal nerve (TN-DCS) elicits responses in the LC region and causes prolonged changes in neural firing, as demonstrated in recent brainstem recording experiments in rats [24]. In humans, external trigeminal nerve stimulation (eTNS) devices, which send pulses to the ophthalmic (or V1) branches in the forehead, are currently used in clinical settings to treat epilepsy [54] and are being investigated for attention-deficit/hyperactivity disorder (ADHD) [54] and depression [55]. Although these devices were developed for therapeutic purposes distinct from tDCS, they both utilize the same bottom-up pathway: trigeminal afferents, the brainstem, and widespread neuromodulation [23]. According to a recent review, trigeminal nerve stimulation has shown potential for enhancing cognition through a bottom-up noradrenergic mechanism; however, outcomes differ, and procedures require refinement [56]. Together, these findings indicate that the trigeminal nerve serves as a vital conduit between the cranium and brain, transforming an electrical stimulus applied at the skin into neurochemical changes within subcortical regions [13]. Numerous tES studies have unintentionally engaged in this pathway [57]. Understanding its function clarifies why tES can have long-lasting effects on mood and memory that extend beyond stimulation, which exemplifies the characteristics of neuromodulator-driven plasticity (such as LC-induced noradrenergic effects), rather than simple electric field perturbation [48]. Importantly, many conventional tES montages place electrodes over regions innervated by trigeminal branches; it is plausible that some protocols partially engage this pathway. However, this

possibility should be evaluated in relation to montage, electrode size, current intensity, and modeled extracranial electric fields, and should not be inferred from nominal current intensity alone.

5. Greater occipital nerve and other peripheral players

The trigeminal nerve is a key component of the new tES framework, but neuromodulation can also be mediated by other peripheral pathways as well [27]. Depending on the electrode montage and current pathways, additional cranial and cervical nerves probably play a role. Cervical nerves such as the GON (a branch of the C2 spinal nerve that innervates the back of the scalp) can be stimulated by tES montages that apply electrodes to the scalp close to the back of the head or neck (for example, stimulating the visual cortex or cerebellum) or any tES montage that has a reference on the mastoid or a return electrode on the neck or shoulder [27]. Similar to trigeminal afferents, GON fibers send sensory information to the brainstem through cervical spinal pathways, which in turn affects LC activity and reticular formation [27]. Vanneste et al. (2020) showed that, in humans, DC stimulation of the GON activated the LC, which in turn improved associative memory by increasing arousal and activating circuits linked to memory. Concurrent changes in the three interconnected proxy indicators of LC-NE activity—pupil diameter, salivary alpha-amylase (sAA), and event-related potentials (ERP)—supported this finding (Fig. 1) [27]. These results were consistent with resting-state fMRI (rsfMRI) findings, which showed that memory-related regions are functionally coupled with stimulation-induced LC activation. Increased connectivity between the LC and the right amygdala and right hippocampus during stimulation, as well as between the LC and the right hippocampus after stimulation, was demonstrated by both seed-based and region-of-interest (ROI)-to-ROI analyses [27]. This improved connectivity most likely represents a neuromodulatory mechanism through which LC-driven arousal improves memory consolidation [27], given the critical role of the amygdala in regulating emotional memory through its dynamic interaction with the hippocampus [54].

6. Vestibular co-activation

Another well-established peripheral route relevant to tES is the vestibular apparatus. As emphasized in the galvanic vestibular stimulation (GVS) literature, weak transcutaneous currents delivered near the mastoids can reliably activate vestibular afferents and alter posture, self-motion perception, gaze control, and vestibular cortical processing. These findings demonstrate that electrical stimulation of the head does not exclusively affect the cortex [58]. A 2010 review explicitly described GVS as a variant of tDCS in which electrodes are placed over the mastoids to stimulate the vestibular system, emphasizing the close conceptual overlap between conventional tES and peripheral vestibular activation [59]. More broadly, recent mechanistic reviews of TES have also listed the vestibular apparatus among the non-cortical structures that can be affected by scalp-applied current [17]. Although vestibular co-activation is not the primary focus of the present review, it should be incorporated into the transcutaneous framework because it can influence perception, autonomic state, balance-related behavior, and potentially experimental blinding depending on montage and current path [60].

7. tACS retinal phosphenes route

Activation of the retinal pathway represents an important peripheral route of tES that cannot be overlooked, particularly in the context of tACS. The manuscript already notes that retinal cells can be activated during tES, as reflected by phosphene reports. Prior work has shown that phosphenes that are activated by electrical stimulation over the visual cortex can originate from the retina instead of the cortex [61]. This is highly supported by evidence from temporal-frequency tuning and electrophysiological recordings obtained near the eye. Recent work has further sharpened this interpretation by arguing that retinal phosphenes are not merely incidental side effects of tACS but important mechanistic confounds, because current spread to the eyes and possibly the optic nerve can alter retinal excitability and, in turn, influence visual processing even below conscious phosphene threshold [62]. Incorporating this retinal pathway into the broader paradigm is thus critical, not just for interpreting visual-system outcomes, but also for sham design, participant blinding, and avoiding overattribution of visual or oscillatory effects to direct cortical entrainment alone.

Together, these observations suggest that multiple peripheral routes may be engaged during tES, with partly distinct downstream consequences. Somatosensory cranial and cervical afferents, such as the trigeminal and greater occipital nerves, may influence cognition through brainstem neuromodulatory nuclei, including the locus coeruleus and dorsal raphe, whereas retinal and vestibular co-activation may more directly affect sensory processing, perception, participant blinding, and interpretation of physiological outcomes. Having outlined these peripheral pathways and their neuroanatomical relationships, we next review animal and human evidence that supports this broader transcutaneous framework.

8. Bridging mechanistic insights from animals to humans

Emphasizing how animal and human trials agree on this concept is essential for embracing the role of neglected peripheral pathways in tES. Here, we summarize the most important data from these fields.

9. Animal studies – causal mechanistic evidence

Animal models have provided direct evidence for the transcutaneous route of neuromodulation [24–27]. In previous studies, the mandibular branch of the trigeminal nerve was stimulated with TN-DCS in anesthetized rats while simultaneously recording brainstem activity [24–26]. In anesthetized rats, applying 0.5-3 mA TN-DCS to the marginal branch of the trigeminal nerve sharply and dose-dependently increased single-unit firing in both the principal sensory (NVsnpr) and mesencephalic (MeV) trigeminal nuclei, whereas conventional scalp tDCS failed to alter their activity [25]. Under the same protocol of TN-DCS, tonic firing rates also significantly increased in both the dorsal raphe nucleus and the LC, while the LC also showed increased phasic bursts (increase in the number of bursts and decrease in the inter-burst intervals), strengthening evidence for a causal link between brainstem arousal centers and peripheral nerve activation [24]. In addition, hippocampal neurons showed downstream changes consistent with increased neuromodulator release [26]. Systemic administration of the adrenergic agonist clonidine abolished the TN-DCS-evoked increase in hippocampal firing, and the same effect was repeated when clonidine was microinjected transcranially into the LC, ruling out off-target effects. After the drug's action had worn off (~60 min), TN-DCS once again elevated the hippocampal spike rate, providing reversible, causal evidence that LC-NE output is necessary to drive the downstream hippocampal response [26]. Behavioral animal studies have also confirmed that activating the cranial/peripheral nerve-LC pathway is necessary to improve the downstream hippocampal response [27,63]. Vanneste et al. implanted a cuff electrode on the GON and demonstrated that short GON-tDCS administered immediately after learning improved long-term memory in rats: treated animals explored novel objects longer and displayed greater inhibitory-avoidance retention 24 h later than sham controls, despite identical acquisition performance [27]. Furthermore, tES-induced alterations in these brain regions were largely eliminated when trigeminal nerve input was blocked by a local anesthetic, highlighting the peripheral origin of the effect [24,26]. These animal findings offer mechanistic evidence that many phenomena commonly attributed to the transcranial route can be reproduced by stimulating cranial/peripheral nerves. They serve as the basis for reinterpreting tES

results in light of peripheral co-stimulation [21].

10. Human studies – Translational and correlative evidence

Although it is not possible to invasively record brainstem activity during tES in humans, the peripheral pathway model is supported by accumulating evidence [55,56]. Based on the assumption that trigeminal-driven LC-NE activation increases arousal, eTNS trials for epilepsy and ADHD have coincidentally reported improvements in mood and cognitive alertness [57,64,65]. Majdi et al. (2023) reassessed the tDCS working-memory literature and suggested that some benefits in working memory tasks may be due to cranial/peripheral nerve co-stimulation, in addition to transcranial effects. They found that electrode placement locations in effective tDCS paradigms often correspond to major nerve distributions, thus predicting cognitive improvements [21]. Subtle physiological, behavioral, and electrophysiological markers in tES subjects that correlate with stimulation periods further imply that brainstem arousal systems are active [66]. The markers are described in detail below.

11. Physiological indicators of LC-NE engagement

11.1. Pupillometry

Pupil diameter is a well-established proxy for LC-NE activity in humans, as LC activation drives sympathetic dilator effects on the pupil [67]. Changes in pupil size that are consistent with LC-NE engagement have been reported in several tES studies [27,63,66]. For example, occipital nerve tDCS (ON-tDCS, which uses electrodes over the C2 dermatome close to the occipital nerve) resulted in a significant pupil dilatation during stimulation (mean pupil area increased from ~12.7 to 13.6 mm^2 under ON-tDCS, versus a slight decrease under sham) when compared to sham [27]. Similarly, a pilot study using a single left prefrontal tDCS session revealed that pupils were noticeably more dilated following active tDCS (post-stimulation pupil size increase, $p < 0.01$) in comparison to baseline and sham conditions [66].

11.2. Salivary alpha-amylase

sAA is an enzyme that is sensitive to adrenergic activity and is often used as a peripheral index of central norepinephrine release [68]. Human fMRI studies have shown that LC activation correlates with rising sAA during arousing experiences [27]. Consistent with LC-NE activation, ON-tDCS in healthy adults significantly elevated sAA levels during (~263 U/mL vs. ~121 U/mL in sham, $p < 0.001$) and immediately after stimulation (~305 U/mL vs. 138 U/mL in sham, $p < 0.001$) compared to sham [27]. Notably, the magnitude of pupil dilation and the increase in sAA were positively correlated across individuals ($R^2 = 0.17$, $p = 0.032$) [27]. Together, the changes in sAA during tES provide biochemical evidence of LC-NE system involvement.

11.3. Other autonomic markers

tES has also been connected to other physiological indicators of arousal. When tES was delivered in phasic "bursts" during a reaction-time task study, skin conductance, which is a gauge of sympathetic activation, was observed. In line with increased autonomic arousal, participants' skin conductance response (SCR) increased concurrently with active stimulation bursts when compared to sham [69]. Although not always stated in detail, the same study found that the heart rate tended to slightly increase with stimulation [69]. Along with pupil and sAA findings, these autonomic alterations clearly show that tES can access brainstem arousal circuits, most likely through LC-NE sympathetic outflow [69].

12. Behavioral and mental effects suggesting LC-NE involvement

12.1. Mood and arousal

Subjective state changes caused by LC-NE activation, which typically increase alertness and, in some cases, improve mood, can be produced by acute tES. Anodal tDCS over the left prefrontal cortex dramatically enhanced the pre-competition mood profile of elite athletes in a placebo-controlled study [70]. Compared with sham, anodal tDCS recipients reported higher vigor, lower tension and fatigue, and reduced anxiety [70]. Another study in stroke patients with fatigue found that active tDCS mitigated subjective fatigue over the course of a task; under sham, participants' self-rated fatigue deteriorated significantly, whereas with real tDCS, they showed no significant increase in fatigue by the session end [66]. These patterns are consistent with an optimal arousal boost, possibly through the noradrenergic pathways.

12.2. Cognitive performance

12.2.1. Sustained attention and reaction time

Mauri et al. showed that arousal can be increased, and attention performance can be enhanced by administering tES bursts time-locked to a continuous performance task [69]. Participants were given short tES currents that matched warning signals during a go/no-go task. Compared to no-stimulation trials, the outcome showed a significant decrease in reaction times during active stimulation bursts, along with an increase in SCR [69]. Faster responses coupled with increased skin conductance indicate enhanced phasic arousal attributable to the recruitment of LC-NE systems that improve alertness [69].

12.2.2. Memory and learning

The LC-NE system is involved in modulating memory consolidation, in part via its projections to the hippocampus and amygdala [71,72]. The transcutaneous LC-NE pathway hypothesis for memory enhancement during tES was directly tested by ON-tDCS during learning [27]. Participants who received ON-tDCS at 1.5 mA during the encoding and early consolidation phases demonstrated better memory performance at retrieval in a face-name association memory paradigm. In particular, the ON-tDCS group had a significantly higher percentage of learned faces than the sham stimulation group (~68% vs. ~58% of faces recognized, $p = 0.013$) [27].

13. Rethinking tES: an integrated conceptual framework

In the updated framework we present, tES functions through two interconnected pathways: a transcutaneous pathway (brainstem neuromodulation via peripheral nerve activation) and a transcranial pathway (electric fields acting on cortical neurons beneath the electrodes) [2]. In most tES applications, these routes most likely occur together; they are not mutually exclusive. Individual anatomical and stimulation parameters (waveform, electrode montage, and intensity) may affect balance. According to our model, the total contribution from both pathways represents the final cognitive or clinical impact of tES [2].

- The transcranial route induces distributed but non-uniform changes in cortical excitability and cortical network dynamics beneath and between electrodes (tDCS) or works by entraining endogenous neural oscillations to the frequency of the applied current, synchronizing the timing of neuronal firing with the stimulation waveform (tACS) [1,10]. This can bias ongoing brain activity across engaged cortical networks, with relatively stronger effects in some regions than others (e.g., slightly biasing a task-related network toward excitation or inhibition) [38].
- The transcutaneous route involves one or more cranial/cervical nerves, which in turn activate deep neuromodulatory systems (LC for noradrenaline, dorsal raphe for serotonin, basal forebrain via NTS for

acetylcholine, etc.) [2]. This leads to a diffuse modulation of the brain state, for instance, elevating arousal, facilitating plasticity, or modulating oscillatory rhythms, which then interact with the cognitive processes of interest [2].

Understanding both pathways guarantees that we create stimulation paradigms that, when necessary, isolate or optimize their synergy (Table 1).

Crucially, our framework explains the need for a review of the sham controls. In an active condition, both routes are continuously engaged, whereas in a typical sham, the transcutaneous route is only slightly activated (a few seconds), and the transcranial route is off [75,76]. Therefore, future research should use better sham conditions that account for peripheral nerve activation (please see the following section). Our integrated model encourages scientists and medical professionals to consider tES as a form of combined brain–nerve stimulation rather than just brain stimulation. This change in perspective may inspire a new experimental design. We believe that this model will encourage the more efficient use of tES because it more accurately represents reality (Fig. 2).

14. Dual-route model in tES: experimental design and control recommendations

To rigorously test and apply the dual-route model, future studies should refine their experimental designs and include new control conditions to isolate each pathway. The key recommendations are as follows:

1. **Nerve-block "sham" condition:** Incorporate a control where peripheral nerve activation is pharmacologically or physically blocked while current is applied. For example, a topical scalp anesthetic can be applied under electrodes to block cutaneous afferents [21]. Under these conditions, any cognitive or neural effects would presumably arise from the transcranial route alone. Initial evidence shows that this approach is feasible: applying lidocaine on the scalp markedly reduces tES effects (e.g., attenuates tremor entrainment by tACS) compared with normal stimulation [13,77]. We recommend including such a "transcranial-only" arm, particularly in studies that aim to make mechanistic claims about direct cortical stimulation, or in paradigms where peripheral co-stimulation is likely to contribute substantially to the observed outcome [77]. This approach may be especially informative when the electrode montage overlaps with major cutaneous afferent territories, for tACS/tDCS studies of arousal, attention, or sensory processing, and for experiments explicitly designed to dissociate transcranial from transcutaneous effects. By contrast, such controls may not be necessary in every tES study, particularly when mechanistic separation of pathways is not the primary aim.
2. **Transcutaneous-only stimulation control:** Conversely, studies can include a condition designed to preferentially engage the relevant cranial or cutaneous afferent pathway while minimizing current flow through the intended cortical target. [24,25]. This control should be anatomically matched to the proposed pathway rather than delivered at an unrelated extracephalic site. For example, when testing whether a frontal tDCS montage partly acts through trigeminal co-stimulation, a focal bipolar montage over another trigeminal branch or nearby cranial cutaneous region could be used to engage trigeminal afferents while avoiding substantial current flow through the frontal cortex. Such a transcutaneous-control condition would allow researchers to test whether activation of a comparable peripheral pathway can reproduce part of the physiological or behavioral effect attributed to the original tES montage [24,25].

Table 1
Empirical underpinnings of the transcranial versus transcutaneous mechanisms of transcranial electrical stimulation. The table lists representative peer-reviewed studies that anchor each side of the dual-mechanism framework.

Evidence supporting the transcranial route	Evidence supporting the transcutaneous route
Weak scalp DC can bidirectionally shift human motor-cortex excitability (anodal ↑, cathodal ↓), consistent with direct cortical modulation [1]	Trigeminal nerve stimulation (TNS) modulates cortical processing: lowers P300 amplitude while maintaining performance, consistent with NE-driven gain control [47]
Early animal intracellular recordings proved that static polarization directly depolarizes/hyperpolarizes cortical neurons [73]	Nightly external TNS improved ADHD symptoms in an RCT; EEG showed frontal theta/beta enhancement (attentional network) [64]
tACS can entrain endogenous cortical oscillations, supporting a direct transcranial influence on neuronal timing [10]	Greater-occipital nerve tES (ON-tES) boosts episodic-memory encoding; salivary α-amylase (sAA) and theta-band EEG increase, linking effect to LC-NE up-regulation [56]
Modern electric-field modelling shows 1 mA tDCS induces ~0.4–0.5 V m^{-1} in cortical tissue—sufficient for local shifts [74]	Burst-mode frontal tES increases skin-conductance responses and shortens reaction times in a continuous-performance task, in line with an LC-mediated alertness improvement [69]

Importantly, we need to note that no single sham or control condition is likely to isolate all forms of peripheral co-activation during tES. Rather, the most appropriate control should be selected according to the stimulation montage, waveform, and primary outcome measure. For example, somatosensory nerve-block or transcutaneous-only control approaches may be informative when testing contributions from trigeminal or greater occipital pathways. Still, these designs would not adequately control for retinal or vestibular co-activation. Studies examining visual or oscillatory outcomes may therefore require phosphene- or retinal-matched controls, whereas montages positioned near the mastoids or posterior head regions should explicitly consider vestibular confounds. Thus, the choice of control condition should be route-specific and guided by the particular peripheral pathway(s) most likely to be engaged in a given experiment.

An additional issue, particularly relevant for studies using neuroimaging endpoints, is that tES may also influence vascular tone and neurovascular coupling [78]. Because BOLD fMRI reflects hemodynamic rather than neural activity directly, stimulation-related changes in the BOLD signal should not automatically be interpreted as evidence of purely neuronal modulation [78]. Recent work suggests that tES may induce both secondary vascular effects through neurovascular coupling and more primary vascular responses involving perivascular nerves and endothelial mechanisms [79]. Consistent with this possibility, ASL-fMRI studies have reported polarity- and intensity-dependent changes in cerebral blood flow during and after tDCS [80]. Thus, in imaging-based studies, especially those relying on BOLD measures, vascular and neurovascular contributions should be considered alongside transcranial and transcutaneous neural mechanisms when interpreting stimulation effects.

15. Future research priorities and open questions

The dual-route model of tES opens up several exciting research directions and unresolved questions that future work should address. As the field moves toward more precise and personalized neuromodulation, investigations should aim to disentangle and exploit both transcranial and transcutaneous contributions in real-time. Key priorities include:

16. Developing real-time biomarkers of tES pathway engagement

Future work should focus on approaches that directly help dissociate transcranial and transcutaneous contributions. Peripheral measures, such as pupil diameter, salivary alpha-amylase, heart rate, and skin

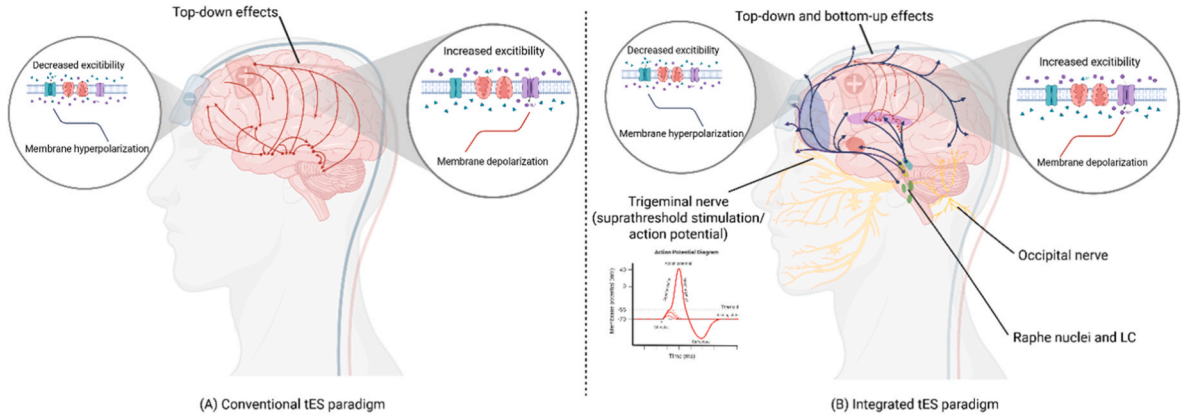

Fig. 2. Conventional versus integrated paradigms for transcranial electrical stimulation (tES). (A) conventional tES model. A cathode (blue, "-") and an anode (red, "+") are placed on the scalp in standard montages to apply weak direct or alternating currents that alter the underlying cortex's membrane polarization. Excitability is decreased by sub-threshold hyperpolarization beneath the cathode and increased by depolarization beneath the anode. These effects are primarily top-down and spread along cortico-cortical networks. (B) The integrated tES paradigm. Peripheral leads engage ascending afferent pathways that project to brain-stem neuromodulatory centers like the locus coeruleus (LC) and raphe nuclei by targeting cranial nerves, as shown here for the trigeminal (yellow) and occipital (yellow) branches, in addition to the cortical electrodes. It is hypothesized that the combination of transcutaneous and transcranial stimulation will couple bottom-up neuromodulatory drive with top-down modulation of cortical circuits, potentially stabilizing and enhancing network-level plasticity. The direction of membrane-potential shifts and a representative change in evoked-potential amplitude (lower right graphs) for each polarity are schematically shown in the insets. LC, locus coeruleus, and tES, transcranial electrical stimulation.

conductance, may provide indirect indices of arousal or sympathetic/noradrenergic engagement, but they do not by themselves establish a central locus coeruleus origin [27]. Central measures, such as EEG or fMRI, can capture cortical oscillatory, evoked, or hemodynamic changes, but these signals may reflect either direct cortical electric-field effects or downstream consequences of peripheral afferent activation. Therefore, route attribution requires combining physiological readouts with appropriate control conditions, such as nerve-block, trans-cutaneous-control, retinal/phosphene-matched, or vestibular-control designs, depending on the montage and outcome measure.

17. Multimodal and computational modeling of dual-route effects

To fully understand and predict tES outcomes, we need models that encompass both the physics of current flow and the physiology of neural systems. Finite element models of tES have advanced our knowledge of electric field distributions in the brain [81,82], but future models should also estimate current densities in the skin and thresholds for peripheral/cranial nerve recruitment. Combining these with neural mass models or network simulations could yield a “systems model” of tES: one that simulates how a given electrode montage produces a certain cortical field (transcranial effect) *and* how it activates specific cranial nerves (transcutaneous effect), and then how those inputs propagate through brain circuits.

18. Conclusion

The tES was located at a critical juncture. What began as a simple method to polarize the cortex has proven to be more complex, involving a network of peripheral pathways connected to the deepest modulatory centers of the brain. This review has traced the journey “from cranium to brain,” demonstrating how electrical currents can travel along cranial nerves to influence memory, learning, and mood via the LC, raphe, and other hubs. Recognizing these overlooked routes is not merely an academic exercise; it is a crucial step in developing, interpreting, and applying tES. We urge cognitive neuroscience and neuromodulation researchers to rethink their approaches to tES in several ways. To accurately assess tES's impact on the brain, we must first acknowledge and control transcutaneous effects. Instead of ignoring the transcutaneous pathways, intentionally focusing on them could enhance the desired outcomes. Additionally, different levels of transcutaneous activation may explain some inconsistent tES results. Educating the clinical community about this framework could alert practitioners to the risk that certain tES montages might unintentionally activate the cranial or peripheral nerves. Understanding this potential can help clinicians to incorporate supplementary considerations into treatment planning, safety assessments, and protocol development. Only by accounting for all the pathways involved in the journey of tES from the cranium to cognitive and behavioral changes can we fully realize its potential.

Author declaration form

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No disclosures relevant to the manuscript.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT in order to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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CRediT authorship contribution statement

Alireza Majdi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Liyi Chen:** Funding acquisition, Visualization, Writing – original draft, Writing – review & editing. **Sven Vanneste:** Conceptualization, Investigation, Supervision, Validation, Writing – review & editing. **Myles Mc Laughlin:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no conflicts of interest to disclose.

References

[1] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527(Pt 3):633–9. Pt 3.
[2] van Boekholdt L, Kerstens S, Khatoun A, Asamoah B, Mc Laughlin M. tDCS peripheral nerve stimulation: a neglected mode of action? Mol Psychiatr 2021;26(2):456–61.
[3] Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol 2003;553(Pt 1):293–301.
[4] Batsikadze G, Moliadze V, Paulus W, Kuo MF, Nitsche MA. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol 2013;591(7):1987–2000.
[5] Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 2001;57(10):1899–901.
[6] Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. Neuroreport 1998;9(10):2257–60.
[7] Costain R, Redfearn JW, Lippold OC. A controlled trial of the therapeutic effect of polarization of the brain in depressive illness. Br J Psychiatry 1964;110:786–99.
[8] Carney MW. Negative polarisation of the brain in the treatment of manic states. Ir J Med Sci 1969;8(3):133–5.
[9] Creutzfeldt OD, Fromm GH, Kapp H. Influence of transcortical d-c currents on cortical neuronal activity. Exp Neurol 1962;5:436–52.
[10] Huang WA, Stitt IM, Negahbani E, Passey DJ, Ahn S, Davey M, et al. Transcranial alternating current stimulation entrains alpha oscillations by preferential phase synchronization of fast-spiking cortical neurons to stimulation waveform. Nat Commun 2021;12(1):3151.
[11] Polanía R, Paulus W, Nitsche MA. Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. Hum Brain Mapp 2012;33(10):2499–508.
[12] Polanía R, Nitsche MA, Korman C, Batsikadze G, Paulus W. The importance of timing in segregated theta phase-coupling for cognitive performance. Curr Biol 2012;22(14):1314–8.
[13] Asamoah B, Khatoun A, Mc Laughlin M. tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. Nat Commun 2019;10(1):266.
[14] Thut G, Schyns PG, Gross J. Entrainment of perceptually relevant brain oscillations by non-invasive rhythmic stimulation of the human brain. Front Psychol 2011;2:170.
[15] Ozen S, Sirota A, Belluscio MA, Anastassiou CA, Stark E, Koch C, et al. Transcranial electric stimulation entrains cortical neuronal populations in rats. J Neurosci 2010;30(34):11476–85.
[16] Fröhlich F, McCormick DA. Endogenous electric fields may guide neocortical network activity. Neuron 2010;67(1):129–43.
[17] Vöröslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernández-Ruiz A, et al. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nat Commun 2018;9(1):483.
[18] Veniero D, Benwell CSY, Ahrens MM, Thut G. Inconsistent effects of parietal α-tACS on pseudoneglect across two experiments: a failed internal replication. Front Psychol 2017;8:952.
[19] Simonsmeier BA, Grabner RH, Hein J, Krenz U, Schneider M. Electrical brain stimulation (tES) improves learning more than performance: a meta-analysis. Neurosci Biobehav Rev 2018;84:171–81.
[20] Grigoreva A, Gorin A, Klyuchnikov V, Dutov I, Moiseeva V, Klucharev V, et al. Effect of transcranial direct current stimulation on FRN and P2 during the performance of an auditory monetary incentive delay task. 2023.
[21] Majdi A, Asamoah B, Mc Laughlin M. Reinterpreting published tDCS results in terms of a cranial and cervical nerve co-stimulation mechanism. Front Hum Neurosci 2023;17:1101490.
[22] Adair D, Truong D, Esmaeilpour Z, Gebodh N, Borges H, Ho L, et al. Electrical stimulation of cranial nerves in cognition and disease. Brain Stimul 2020;13(3):717–50.
[23] Liu A, Vöröslakos M, Kronberg G, Henin S, Krause MR, Huang Y, et al. Immediate neurophysiological effects of transcranial electrical stimulation. Nat Commun 2018;9(1):5092.
[24] Majdi A, Chen L, Larsen LE, Raedt R, Laughlin MM. tDCS cranial nerve Co-stimulation: unveiling brainstem pathways involved in trigeminal nerve direct current stimulation in rats. Brain Stimul 2025;18(2):171–84.
[25] Majdi A, Asamoah B, Mc Laughlin M. Understanding novel neuromodulation pathways in tDCS: brain stem recordings in rats during trigeminal nerve direct current stimulation. Transl Psychiatry 2024;14(1):456.
[26] Chen L, Deng Z, Asamoah B, Laughlin MM. Trigeminal nerve direct current stimulation causes sustained increase in neural activity in the rat hippocampus. Brain Stimul 2024;17(3):648–59.
[27] Vanneste S, Mohan A, Yoo HB, Huang Y, Luckey AM, McLeod SL, et al. The peripheral effect of direct current stimulation on brain circuits involving memory. Sci Adv 2020;6(45).
[28] Lescrauwaet E, Sprengers M, Carrette E, Algoet C, Mertens A, Klooster D, et al. Investigating the working mechanism of transcranial direct current stimulation. Neuromodulation 2025;28(1):68–75.
[29] Seminck N, Khatoun A, Kerstens S, Nuttin B, Mc Laughlin M. External stimulation of the trigeminal nerve causes pupil dilation in healthy volunteers, suggesting locus coeruleus modulation. Brain Stimul 2024;17(3):678–80.
[30] Kar K, Krekelberg B. Transcranial electrical stimulation over visual cortex evokes phosphenes with a retinal origin. J Neurophysiol 2012;108(8):2173–8.
[31] Martinsen ØG, Grimnes S, Piltan H. Cutaneous perception of electrical direct current. ITBM-RBM 2004;25(4):240–3.
[32] Thiele C, Zaehle T, Haghikia A, Ruhnau P. Amplitude modulated transcranial alternating current stimulation (AM-TACS) efficacy evaluation via phosphene induction. Sci Rep 2021;11(1):22245.
[33] Karabanov AN, Saturnino GB, Thielscher A, Siebner HR. Can transcranial electrical stimulation localize brain function? Front Psychol 2019;10:213.
[34] Minhas P, Datta A, Bikson M. Cutaneous perception during tDCS: role of electrode shape and sponge salinity. Clin Neurophysiol 2011;122(4):637–8.
[35] Turi Z, Ambrus GG, Ho KA, Sengupta T, Paulus W, Antal A. When size matters: large electrodes induce greater stimulation-related cutaneous discomfort than smaller electrodes at equivalent current density. Brain Stimul 2014;7(3):460–7.
[36] Kasten FH, Duecker K, Maack MC, Meiser A, Herrmann CS. Integrating electric field modeling and neuroimaging to explain inter-individual variability of tACS effects. Nat Commun 2019;10(1):5427.
[37] Li LM, Uehara K, Hanakawa T. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. Front Cell Neurosci 2015;9:181.
[38] Nitsche MA, Koschack J, Pohlers H, Hullemann S, Paulus W, Happe S. Effects of frontal transcranial direct current stimulation on emotional state and processing in healthy humans. Front Psychiatr 2012;3:58.
[39] Petrocchi N, Piccirillo G, Fiorucci C, Moscucci F, Di Iorio C, Mastropietri F, et al. Transcranial direct current stimulation enhances soothing positive affect and vagal tone. Neuropsychologia 2017;96:256–61.
[40] Bjekić J, Živanović M, Stanković M, Paunović D, Konstantinović U, Filipović SR. The subjective experience of transcranial electrical stimulation: a within-subject comparison of tolerability and side effects between tDCS, tACS, and otDCS. Front Hum Neurosci 2024;18:1468538.
[41] Greinacher R, Buhôt L, Möller L, Learmonth G. The time course of ineffective sham-blinding during low-intensity (1 mA) transcranial direct current stimulation. Eur J Neurosci 2019;50(8):3380–8.
[42] Nelson JT, McKinley RA, Golob EJ, Warm JS, Parasuraman R. Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). Neuroimage 2014;85(Pt 3):909–17.
[43] Turnbull A, Anthony M, Tadin D, Porsteinsson AP, Heffner K, Lin FV. Effect of online tDCS to left somatomotor cortex on neuropsychiatric symptoms among older adults at risk for dementia. Cortex 2023;159:131–41.
[44] Chen L, Majdi A, Asamoah B, Mc Laughlin M. Neural mechanisms of tDCS: insights from an in-vivo rodent model across a range of electric field strengths. Brain Stimul 2026;19(2):103053.
[45] Woolfall P, Coulthard A. Pictorial review: trigeminal nerve: anatomy and pathology. Br J Radiol 2001;74(881):458–67.
[46] Menétrey D, Basbaum AI. Spinal and trigeminal projections to the nucleus of the solitary tract: a possible substrate for somatovisceral and viscerovisceral reflex activation. J Comp Neurol 1987;255(3):439–50.
[47] Tramonti Fantozzi MP, Artoni F, Di Galante M, Briscese L, De Cicco V, Bruschini L, et al. Effect of the trigeminal nerve stimulation on auditory event-related potentials. Cereb Cortex Commun 2021;2(2):tgab012.
[48] Noei S, Zouridis IS, Logothetis NK, Panzeri S, Totah NK. Distinct ensembles in the noradrenergic locus coeruleus are associated with diverse cortical states. Proc Natl Acad Sci U S A 2022;119(18):e2116507119.
[49] Maity S, Rah S, Sonenberg N, Gkogkas CG, Nguyen PV. Norepinephrine triggers metaplasticity of LTP by increasing translation of specific mRNAs. Learn Mem 2015;22(10):499–508.
[50] Titulaer J, Björkholm C, Feltmann K, Malmlöf T, Mishra D, Bengtsson Gonzales C, et al. The importance of ventral hippocampal dopamine and norepinephrine in recognition memory. Front Behav Neurosci 2021;15:667244.
[51] Palacios-Filardo J, Mellor JR. Neuromodulation of hippocampal long-term synaptic plasticity. Curr Opin Neurobiol 2019;54:37–43.
[52] Mather M, Clewett D, Sakaki M, Harley CW. Norepinephrine ignites local hotspots of neuronal excitation: how arousal amplifies selectivity in perception and memory. Behav Brain Sci 2016;39:e200.
[53] Unsworth N, Robison MK. A locus coeruleus-norepinephrine account of individual differences in working memory capacity and attention control. Psychon Bull Rev 2017;24(4):1282–311.

[54] McReynolds JR, Anderson KM, Donowho KM, McIntyre CK. Noradrenergic actions in the basolateral complex of the amygdala modulate Arc expression in hippocampal synapses and consolidation of aversive and non-aversive memory. Neurobiol Learn Mem 2014;115:49–57.
[55] Byczynski G, Farrelly R, Dempsey E, Scarlat IM, Vanneste S. Occipital nerve stimulation selectively modulates top-down inhibitory control. Brain Stimul 2025;18(1):97–9.
[56] Arulchelvan E, Vanneste S. Transcutaneous electrical stimulation enhances episodic memory encoding via a noradrenaline-attention network, with associated neuroinflammatory changes. Brain Stimul 2025;18(1):191–207.
[57] Gil-López F, Boget T, Manzanares I, Donaire A, Conde-Blanco E, Baillés E, et al. External trigeminal nerve stimulation for drug resistant epilepsy: a randomized controlled trial. Brain Stimul 2020;13(5):1245–53.
[58] Pires A, Silva TR, Torres MS, Diniz ML, Tavares MC, Gonçalves DU. Galvanic vestibular stimulation and its applications: a systematic review. Braz J Otorhinolaryngol 2022;88(Suppl 3) (Suppl 3):S202-s11.
[59] Utz KS, Dimova V, Oppenländer K, Kerkhoff G. Electrified minds: transcranial direct current stimulation (tDCS) and galvanic vestibular stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology–a review of current data and future implications. Neuropsychologia 2010;48(10):2789–810.
[60] Dlugaiczyk J, Gensberger KD, Straka H. Galvanic vestibular stimulation: from basic concepts to clinical applications. J Neurophysiol 2019;121(6):2237–55.
[61] Schutter DJ, Hortensius R. Retinal origin of phosphenes to transcranial alternating current stimulation. Clin Neurophysiol 2010;121(7):1080–4.
[62] Schutter D, Wischnewski M, Paternò S, Smits FM. More than meets the eye: retinal phosphenes as confounds in transcranial alternating current stimulation. Int J Psychophysiol 2025;218:113285.
[63] Luckey AM, McLeod LS, Huang Y, Mohan A, Vanneste S. Making memories last using the peripheral effect of direct current stimulation. eLife 2023;12.
[64] Rubia K, Johansson L, Carter B, Stringer D, Santosh P, Mehta MA, et al. The efficacy of real versus sham external trigeminal nerve stimulation (eTNS) in youth with attention-Deficit/Hyperactivity disorder (ADHD) over 4 weeks: a protocol for a multi-centre, double-blind, randomized, parallel-group, phase IIb study (ATTENS). BMC Psychiatry 2024;24(1):326.
[65] Ma H, Fan S, Xu Z, Wan X, Yang Q, Yin Y, et al. Trigeminal nerve stimulation for prolonged disorders of consciousness: a randomized double-blind sham-controlled study. Brain Stimul 2023;16(3):819–27.
[66] Rembrandt HN, Riley EA. Evidence of physiological changes associated with single-session pre-frontal tDCS: a pilot study. Front Hum Neurosci 2025;19:1549248.
[67] Joshi S, Li Y, Kalwani RM, Gold JI. Relationships between pupil diameter and neuronal activity in the locus coeruleus, Colliculi, and cingulate cortex. Neuron 2016;89(1):221–34.
[68] Schneider C, Priovoulos N, Prokopiou PC, Verhey FR, Poser BA, Ivanov D, et al. Locus coeruleus fMRI response to transcutaneous auricular vagus nerve stimulation is coupled to changes in salivary alpha amylase. Brain Stimul 2025;18(4):1205–7.
[69] Mauri P, Miniussi C, Balconi M, Brignani D. Bursts of transcranial electrical stimulation increase arousal in a continuous performance test. Neuropsychologia 2015;74:127–36.
[70] Mehrsafar AH, Rosa MAS, Zadeh AM, Gazerani P. A feasibility study of application and potential effects of a single session transcranial direct current stimulation (tDCS) on competitive anxiety, mood state, salivary levels of cortisol and alpha amylase in elite athletes under a real-world competition. Physiol Behav 2020;227:113173.
[71] Giustino TF, Maren S. Noradrenergic modulation of fear conditioning and extinction. Front Behav Neurosci 2018;12:43.
[72] Jacobs HI, Priovoulos N, Poser BA, Pagen LH, Ivanov D, Verhey FR, et al. Dynamic behavior of the locus coeruleus during arousal-related memory processing in a multi-modal 7T fMRI paradigm. eLife 2020;9.
[73] Purpura DP, McMurtry JG. Intracellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol 1965;28:166–85.
[74] Yoon MJ, Park HJ, Yoo YJ, Oh HM, Im S, Kim TW, et al. Electric field simulation and appropriate electrode positioning for optimized transcranial direct current stimulation of stroke patients: an in silico model. Sci Rep 2024;14(1):2850.
[75] Kessler SK, Turkeltaub PE, Benson JG, Hamilton RH. Differences in the experience of active and sham transcranial direct current stimulation. Brain Stimul 2012;5(2):155–62.
[76] Fonteneau C, Mondino M, Arns M, Baeken C, Bikson M, Brunoni AR, et al. Sham tDCS: a hidden source of variability? Reflections for further blinded, controlled trials. Brain Stimul 2019;12(3):668–73.
[77] Kerstens S, Orban de Xivry JJ, Mc Laughlin M. A novel tDCS control condition using optimized anesthetic gel to block peripheral nerve input. Front Neurol 2022;13:1049409.
[78] Keilholz SD, Pan WJ, Billings J, Nezafati M, Shakil S. Noise and non-neuronal contributions to the BOLD signal: applications to and insights from animal studies. Neuroimage 2017;154:267–81.
[79] Bahr-Hosseini M, Bikson M. Neurovascular-modulation: a review of primary vascular responses to transcranial electrical stimulation as a mechanism of action. Brain Stimul 2021;14(4):837–47.
[80] Jamil A, Batsikadze G, Kuo HI, Meesen RLJ, Dechent P, Paulus W, et al. Current intensity- and polarity-specific online and aftereffects of transcranial direct current stimulation: an fMRI study. Hum Brain Mapp 2020;41(6):1644–66.
[81] Indahlastari A, Chauhan M, Sadleir RJ. Benchmarking transcranial electrical stimulation finite element models: a comparison study. J Neural Eng 2019;16(2):026019.
[82] Neuling T, Wagner S, Wolters CH, Zaehle T, Herrmann CS. Finite-element model predicts current density distribution for clinical applications of tDCS and tACS. Front Psychiatr 2012;3:83.