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REVIEW ARTICLE

Direct current stimulation as a non-invasive therapeutic alternative for treating autonomic or non-autonomic neurological disorders affecting breathing

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Abstract
Direct current stimulation (DCS) is a non-invasive approach to stimulate the nervous system that is now considered a powerful tool for treating neurological diseases such as those affecting cognitive or locomotor functions. DCS, as applied clinically today, is an approach built on early uses in antiquity and knowledge gained over time. Its current use makes use of specific devices and takes into account knowledge of the mechanisms by which this approach modulates functioning of the nervous system at the cellular level. Over the last 20 years, although there are few studies, it has been shown that DCS can also modulate the breathing autonomic function. In this narrative review, after briefly providing the historical perspective and describing the principles and the main cellular and molecular effects, we summarize the currently available data regarding the modulation of ventilation, and propose that DCS could be used to treat autonomic or non-autonomic neurological disorders affecting breathing.

Keywords Central respiratory drive · Neuromodulation · Neurorespiratory disorders · Noninvasive brain or spinal stimulation · Electrical current

Introduction

Breathing, whose main role is to enable the exchange of gases between the internal and external environments and thus ensure homeostasis through a continuous supply of O_2, is an autonomous function. Autonomic functions, which ensure the body's homeostasis, depend on neurovegetative regulation coordinated with somatic or hormonal processes. So, while the afferent neural control of breathing is associated with the autonomic nervous system, its efferent side is part of the somatic nervous system. The central ventilatory drive relies on two components (Fig. 1). First, an automatic component that depends on a network of neurons located in the brainstem, including rhythm generators, structures involved in "central ventilatory chemoreception" (detection of changes in CO_2/H^+ and the associated effects on breathing) and structures that integrate the rhythm from generators and changes in CO_2/H^+ and O_2 into a command transmitted to motoneurons innervating ventilatory and upper airway muscles (Fig. 1A–C) [28, 73]. Second, a voluntary or behavioral component which has a suprapontine origin, allowing an adjustment of ventilation during voluntary or behavioral activities and also in certain pathophysiological situations (Fig. 1A, B) [19, 24, 29, 71, 79]. These two components interact to establish a rhythmic command which, in a healthy context, is adapted to the body's needs and transmitted to motoneurons innervating respiratory muscles (Fig. 1A, B). Some pathologies of neurological (autonomic and/or somatic) or mixed neurological/peripheral origin affecting breathing, such as central hypoventilation, sleep apnea, or spinal cord injury, have few or no available therapies and result in inadequate ventilation [8, 41]. It is in this context that certain data obtained over the past 20 years have demonstrated that direct current stimulation (DCS) applied to the brain or spinal cord can modulate breathing, suggesting its

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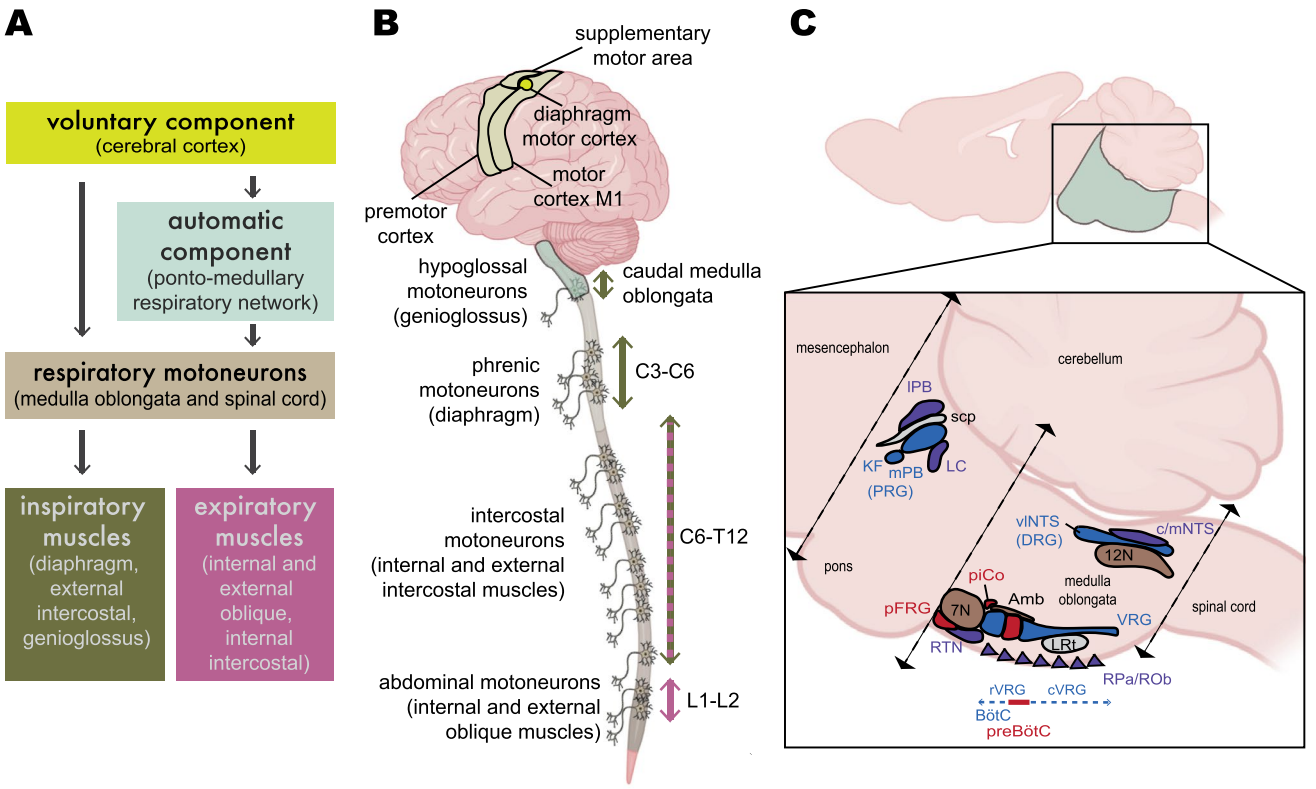

Fig. 1 Functional and anatomical organization of the central ventilatory command. Breathing depends on a central command that comprises two components, an automatic component elaborated in a ponto-medullary ventilatory network, and a voluntary or behavioral component originating from motor cortical areas; this command causes rhythmic contraction of the respiratory muscles of the thoracic cage and upper airways (**A**, **B**). The ponto-medullary ventilatory neuronal network has been characterized in detail in rodents in recent years (**C**). Abbreviations: 7N, facial nucleus; 12N, hypoglossal nucleus; Am, ambiguus nucleus; BötC, Bötzinger complex; c/mNTS, commissural and median parts of the nucleus of the solitary tract; cVRG, caudal ventral respiratory group; DRG, dorsal respiratory group; KF, Kolliker-Füse; lPB, lateral part of the parabrachial nucleus; LC, locus coeruleus; LRt, lateral reticular nucleus; mBP, median part of the parabrachial nucleus; pFRG, parafacial respiratory group; piCo, post-inspiratory complex; preBötC, pre-Bötzinger complex; PRG, pontine respiratory group; ROb, raphe obscurus nucleus; RPa, raphe pallidus nucleus; RTN, retrotrapezoid nucleus; scp, superior cerebellar peduncle; rVRG, rostral ventral respiratory group; vlNTS, ventrolateral subdivision of the nucleus of the solitary tract; VRG, ventral respiratory group. **A**, adapted from "brain (lateral view)", "lateral spinal cord", and "multipolar neuron, motor, curved"; **B**, adapted from "mouse brain (sagittal cut)" by BioRender.com 2024, retrieved from https://app.biorender.com/biorender-templates

future clinical use in the aforementioned pathophysiological situations.

Electrical currents as a therapeutic tool: from the historical use of the torpedo fish to the contemporary use of DCS procedures

Historical perspective

Electrical currents have been used as a therapeutic tool since start of the Common Era (CE). As reported, in 43–48 CE, Scribonius Largus used the electrical properties of the torpedo fish to treat patients suffering from gout and headaches [37]. However, it was not until the eighteenth century that the topic became a subject of study in biology, with the study of torpedo fish by John Walsh in 1773, whose work led to many discoveries by Luigi Galvani and Alessandro Volta [81]. Knowledge of the electrical properties of nerve cells led to the first applications of direct currents (DC) [3, 5]. In the early twentieth century, DCS at the transcranial level (transcranial DCS) started to be used, mainly in Russia, with electrosleep approaches, which consisted of stimulating the brains of patients who had suffered morphine poisoning [65]. In 1977, the US Food and Drug Administration (FDA) classified DCS as a class III device (defined by the FDA as a device for sustaining or supporting life that is high risk for the patient/user and requires premarket approval) used for insomnia, anxiety, and depression [25, 72].

Emergence of new psychiatric drugs in first half of the twentieth century had a negative impact on the interest in DCS up until the 1990s, after which DC regained significant

interest as knowledge of the nervous system improved [59]. Discoveries in the late 1990s and throughout the 2000s, such as modulation of cortical excitability with low intensity stimulation through the scalp, were the basis for what is considered to be modern DCS [14, 39, 53].

Basic principles of DCS as used today

DCS consists of delivering an electrical current from an active (or target) electrode to a reference (or return) electrode. The active electrode must be as close as possible to the region of interest; the reference electrode must be placed appropriately to achieve the desired current flow direction. The positioning of electrodes is a determining factor in obtaining the desired effects, since the most intense stimulation is obtained in tissue that is closest to the active electrode [25]. The electrode through which a positive current enters the body is the anode, and the electrode through which the positive current leaves the body is the cathode. If the active electrode is an anode (positively charged because it is connected to the positive pole of the generator), stimulation is referred to as anodal (Fig. 2); if the active electrode is a cathode (negatively charged because it is connected to the negative pole of the generator), the stimulation is referred to as cathodal (Fig. 2). As specified above, if DCS is applied at the cephalic level, it is called transcranial DCS; if applied to the skin at the level of the spinal cord, it is called transcutaneous spinal DCS (Fig. 2).

With the anatomical differences between the brain or spinal structures and between individuals, it is important to take the electric field induced by transcranial DCS/transcutaneous spinal DCS into account as the waveform direction and current strength can be detected up to a certain distance from the electrodes [35]. The distribution of current densities has been explored using models such as a sphere model for the head or a more realistic model such as that obtained with human magnetic resonance imaging, which takes into account the different tissues crossed by the current [21, 69]. The change in electrode size induced changes in the spatial distribution of current whereas a change in the current results in a change in field amplitude. Highest current densities were always observed under the active or reference electrode, but close densities were obtained in other areas of the brain, implying that observed effects may depend on the invasion of regions of the nervous system other than the primary targets.

Safety for the application of DCS

Numerous studies have characterized the conditions of use of DCS in humans, i.e., limitation of stimulation parameters for safe use and precautions associated with certain pathologies or pharmacological treatments. As reviewed by Bikson and colleagues, use of conventional DCS protocols in human trials ($\leq$4 s to 40 min, $\leq$0.1 to 4 mA) has not produced any reports of a serious adverse effect (damage of brain tissue, significant, persistent, or permanent unwanted change in the patient's body function/structure or quality of life) across over 33,200 sessions and 1000 subjects with repeated sessions [9]. However, there are specific recommendations for certain pathological situations. Notably, even though with intensities $\leq$4 mA transcranial DCS has been to be safe in treatment of strokes, to avoid adverse effects it is recommended to diminish the administration of anti-epileptic drugs prior to transcranial DCS sessions to avoid any risks of modulating the medication action [13].

Neurobiological mechanisms of DCS

DCS leads to non-invasive neuromodulation of central nervous system functioning by immediate effects and long-term synaptic plasticity that follows general mechanisms of long-term potentiation/long-term depression. DCS also appears to be responsible for neuroprotective effects. These different effects are linked to effects on neurons, glial cells, or both.

Anodal or cathodal transcranial DCS, opposite effects on neuronal cell excitability in cortical and spinal cord regions

DCS modulates neuronal cell excitability, i.e., it changes the synaptic strength between neurons but does not modify the nature of neuronal connections [63]. When the electrical field induced by DCS reaches the membrane of one of the compartments of the neuron, it will change the polarization of that portion of the membrane [16, 33, 48, 60, 62] (Fig. 2). At the level of a single neuron, the effect of DCS depends on the distance to the electrodes and the orientation of axonal arborization; these elements underpin the opposing effects of anodal and cathodal DCS between cerebral cortical areas and spinal cord (Fig. 2). Numerous studies carried out at the cortical level have established that anodal transcranial DCS increases neuronal excitability, while cathodal transcranial DCS decreases it [20, 32, 36]. Although far fewer studies have been carried out in the spinal cord than in brain cortical regions, data reported indicate that at the level of spinal cord, the influence of anodal vs cathodal transcutaneous spinal DCS is reversed from that described in the cortex. Facilitation of the corticospinal pathway and somatosensory evoked potentials by peripheral nerve stimulation is under cathodal but not anodal configuration, with cathodal transcutaneous spinal DCS enhancing and anodal transcutaneous spinal DCS reducing the firing rate of spinal neurons by respectively depolarizating or hyperpolarizating effects [1, 15, 74, 82].

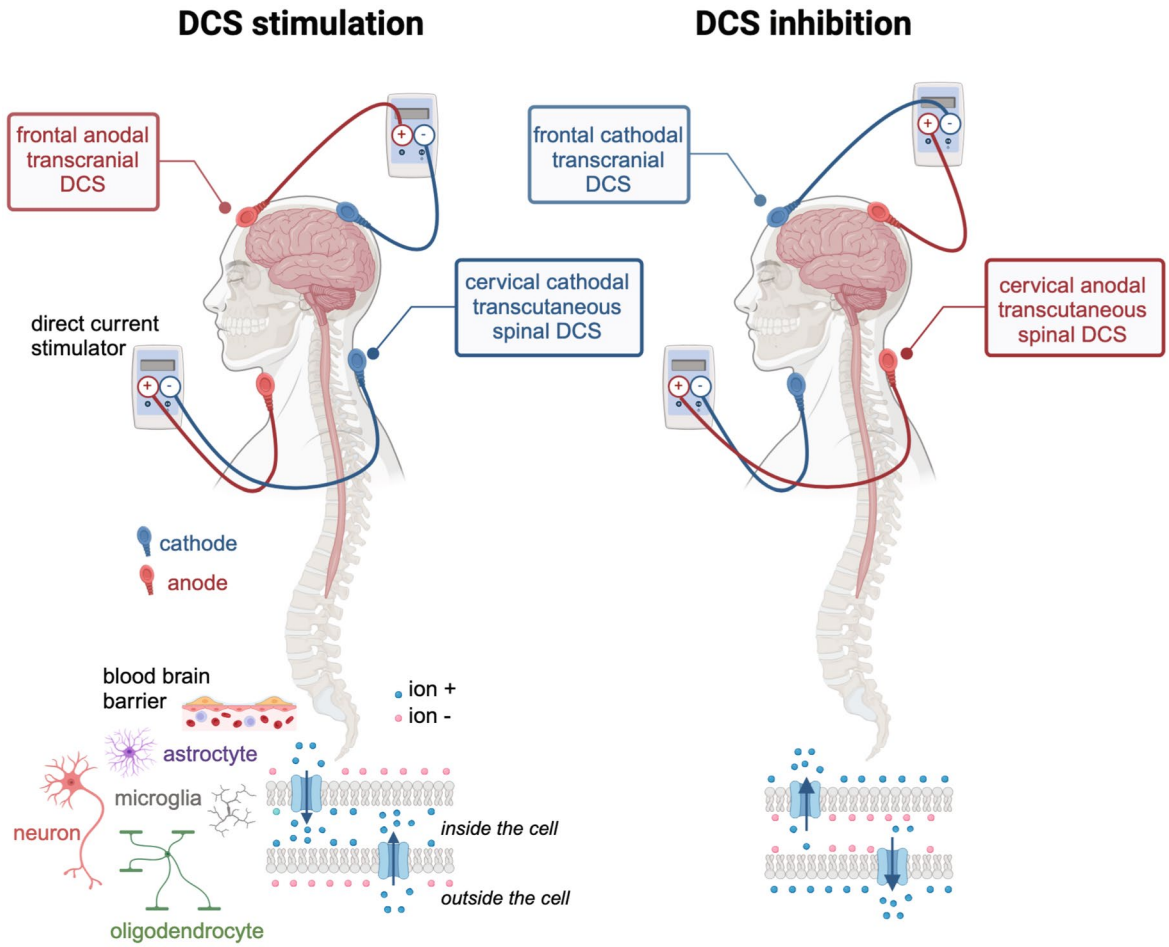

Fig. 2 Anodal and cathodal DCS and their respective effect on membrane polarization depending on the region of the central nervous system targeted. DCS is a non-invasive nervous system stimulation technique that consists of delivering a weak electrical current. If DCS is applied to the skin at the cephalic level, it is called transcranial DSC or transcranial DCS; if applied to the skin in front of the spinal cord, it is called transcutaneous spinal DCS. Two types of stimulation are possible, anodal or cathodal. The electrode through which a positive current enters the body is an anode (positively charged because connected to the positive pole of the generator) and the electrode through which the positive current leaves the body is a cathode (negatively charged because connected to the negative pole of the generator). Stimulation is named anodal when the anode is the electrode closest to the area of interest; conversely, if the cathode is the electrode closest to the zone of interest, stimulation is named cathodal. The weak current used leads to changes in membrane polarity that can result in either depolarization (and thus a stimulating effect) or hyperpolarization (and thus an inhibiting effect). On the left, configurations giving rise to membrane depolarization, i.e., anodal for the brain (the frontal cortex is the target in the illustrated example) and cathodal for the spinal cord (cervical segments are the target in the illustrated example). On the right, configurations giving rise to membrane hyperpolarization, i.e., cathodal for the brain and anodal for the spinal cord. All cell types present in the central nervous system can be modulated by DCS: neurons, astrocytes, microglia and also cells of the blood–brain barrier or oligodendrocytes, (although little data is yet available for the last two). Adapted from "brain (lateral view)", "spine(lateral)", "spinal cord (lateral, no nerve)", "adult male head (lateral, hairless)", "transcranial DCS device", "motor neuron (curved) 3", "microglia 2", "astrocyte" by BioRender.com 2024, retrieved from https://app.biorender.com/biorender-templates

Chemical synaptic remodeling

A growing number of animal and human studies in recent years have revealed DCS-induced changes in glutamatergic and GABAergic neurotransmission. Anodal transcranial DCS increases cortical excitability by an increase in synaptic strength involving NMDA or AMPA receptors, e.g., in the hippocampus [2, 66, 75]. The induction of plasticity with anodal transcranial DCS is enhanced in the presence of an NMDA agonist, while it is inhibited in the presence of an NMDA blocker [49]. Taking GABAergic systems as an example, after repeated anodal trans-spinal DCS a reduction of spasticity has been reported concomitant with a down-regulation of the cotransporter NKCC1 involved in entry of Cl^- into cells and thus in GABA/$GABA_A$ [42]. Administration of lorazepam, an allosteric $GABA_A$ modulator, enhances and prolongs the effects of anodal transcranial DCS [52]. In addition, monoaminergic systems have also been reported to

be affected by DCS, e.g., anodal transcranial DCS stimulations have been shown to modulate dopaminergic systems and enhance serotonin transmission [23, 34, 50, 51].

Neurotrophins and other factors involved in synaptic functioning have been described to be modulated by transcranial DCS. It has been reported that anodal transcranial DCS increases the level of BDNF, expression of *cFOS* or *CREB*, and quantity of synapsin and CaMKII in the cortex or hippocampus in rats [31], and improves hearing ability of hearing-impaired rats through denser synapses and better synaptic transmissions related to increased levels of synaptophysin and BDNF [54].

Neurogenesis and neuronal migration

Evidence for cell proliferation has been observed under transcranial DCS applications in rodents: cathodal but not anodal transcranial DCS increased the number of proliferative cells and the number of neural stem cells on the ipsilateral side to the stimulation [67], transcranial DCS promoted cell proliferation and increased the number of neuroblasts on the ipsilateral side exposed to ischemic stroke whether anodal or cathodal [10], and two sessions of five consecutive days of cathodal transcranial DCS increased neurogenesis in both sides of the brain, whereas anodal transcranial DCS increased the number of neuroblasts only on the ipsilateral side to the stimulation [56]. Similar results were obtained with transcutaneous spinal DCS applied to the lumbar spinal cord [70].

Influences of DCS on glial cells

In 2012, the idea emerged that DCS could act not only on neurons but also on glial cells (Fig. 2) [68]. DCS induces a considerable surge of Ca^{2+} in cortical astrocytes that contributes to synaptic plasticity [45] and induces gene upregulation, which may constitute a glial-mediated plasticity pathway in cultured astrocytes [11]. Few studies have focused on the involvement of oligodendrocytes in DCS-induced plasticity (Fig. 2). However, it seems that cathodal DCS induces migration of oligodendrocyte precursors towards ischemic regions, where they allow remyelination [10], and transcutaneous spinal DCS has been reported to increase the number of oligodendrocyte progenitor cells [70]. Finally, some recent data support a modulation of microglial cells: anodal transcranial DCS increases microglial motility and migration [26] and in a stroke context it was observed that transcranial DCS regulates the phenotype transition of microglia [10]. Since neuroinflammation is negatively correlated to neuroplasticity, microglia constitute an interesting target for the prevention of long-term inflammation following tissue damage [27].

Anatomical and functional basis of central ventilatory control

Breathing depends on a central command that causes rhythmic contraction of the respiratory muscles of the thoracic cage, inspiratory muscles (diaphragm, external intercostal muscles), expiratory muscles (internal and external oblique and internal intercostal muscles), and upper airways muscles (genioglossus; Fig. 1A). Central ventilatory drive comprises two components: an automatic component elaborated in a ponto-medullary ventilatory network, and a voluntary or behavioral component originating from motor cortical areas (Fig. 1A, B) [19, 24, 28, 29, 71, 73]. While the automatic component is transmitted directly to respiratory motoneurons controlling ventilatory muscles, the voluntary or behavioral component can either be transmitted directly to these motoneurons or to the brainstem respiratory network (Fig. 1A). Ventilatory motoneurons innervating muscle of the thoracic cage are located in cervical (phrenic motoneurons), thoracic (internal and external intercostal motoneurons), and lumbar (internal and external abdominal motoneurons) segments of the spinal cord (Fig. 1B); those innervating the tongue genioglossus muscle are located in caudal medulla oblongata (hypoglossal motoneurons, Fig. 1B). The brainstem ventilatory neuronal network has been characterized in detail in rodents in recent years (Fig. 1C), but its precise characterization in humans is not yet fully established. It contains three respiratory rhythm generators in the ventral part of medulla oblongata: the pre-Bötzinger complex, considered as the inexorable generator of inspiration, and the parafacial respiratory group and post-inspiratory complex, both considered as conditional generators for expiration and post-inspiration, respectively. Rhythmic activity emerging from the interaction between the three respiratory generators is integrated in functional groups: the ventral respiratory group (a ventral column comprising the Bötzinger complex in its rostral part, and the reticular formation in alignment with the pre-Bötzinger complex in its caudal part), the dorsal respiratory group (corresponding to the ventrolateral subdivision of the nucleus of the solitary tract), and the pontine respiratory group (corresponding to the median subdivision of the parabrachial and Kolliker-Füse nucleus). Respiratory rhythm generators and/or functional ventral, dorsal, and pontine respiratory groups are permanently subject to chemosensitive inputs from brainstem CO_2/H^+ sensitive structures (main, retrotrapezoid nucleus and secondary, raphe pallidus and obscurus, locus coeruleus) or from brainstem structures relaying CO_2/H^+ or O_2 chemosensitive information from peripheral (commissural and median subdivisions of the nucleus of the solitary tract) or suprapontine sources (lateral subdivision of the parabrachial nucleus).

Modulation of breathing by DCS

It is possible that breathing is modulated by DCS. This is supported by considerable evidence from the last 20 years that this function depends on a neural network displaying plasticity, whether in the automatic control emerging from the brainstem, in the cortical component of ventilatory control, or in motoneurons innervating the respiratory muscles of the thoracic cage or upper airways [18, 44, 46, 77].

Transcranial DCS application at the cephalic level in healthy subjects

The first studies to report a link between DCS and ventilation date back to the 1960s, when Lippold and colleagues described apnea followed by a decrease in respiratory frequency (f_R) in a healthy volunteer subjected to a 3 mA session of cathodal DCS applied to the frontal cortex with an extra-encephalic reference electrode (Table 1) [40, 64]. The authors suggested that these respiratory effects were linked to the passage of current through the brainstem, since the observed effect corresponded to an alteration in respiratory rhythm, an element directly dependent on respiratory rhythm generators or, more broadly, the respiratory neuronal network in the brainstem (Fig. 1).

Although this initial observation could suggest that this approach might lead to potentially dangerous respiratory effects or, on the contrary, that it could provide a new means of non-invasively exploring the respiratory neural network in humans, in the years that followed numerous studies explored the effects of transcranial DCS on various functions, with no mention of the possible effects on ventilatory control. It was not until 2010 that the effect of this type of intervention on ventilatory drive was explored [80], with no observed effect of either anodal or cathodal configurations on f_R (with no mention of tidal volume analysis) using a DCS configuration close to that used in the 1960s. In addition to modest differences in electrode positioning, the stimulation parameters chosen differed to those used in the first studies, and corresponded to those used in the majority of studies at the time (Table 1). It is therefore quite plausible that it is the difference in current intensity between these studies, separated by almost 50 years, that is at the root of these divergent effects. In line with the idea that a lack of effect is linked to low current intensity in brainstem regions containing the respiratory neural network, Parazzini and colleagues assessed current density in the brainstem using the setup developed by Vandermeeren and colleagues in 2010 [55, 80]. They used three realistic human models and concluded that current density was low in the medulla oblongata and pons [55].

Shortly after the study of Vandermeeren and collaborators, two other teams explored the effect of transcranial DCS on ventilation or its nerve pathways using "cephalic-cephalic" configurations. One of these studies concluded that transcranial DCS had no effect on f_R (again without analysis of tidal volume); the active electrode (anode) was positioned over the C3 position and the reference over the right supraorbital region (Table 1) [61]. The absence of a breathing effect can be interpreted as associated with the absence of electric field propagation to rhythm generators in the brainstem. The second study examined the effect of transcranial DCS applied to the motor cortex on excitability of the diaphragmatic corticospinal pathway [7]. The active electrode was placed over the left diaphragmatic primary cortex (Table 1). The authors observed that in both anodal and cathodal configurations, transcranial DCS led to a decrease in amplitude of right hemidiaphragm motor-evoked potentials in response to transcranial magnetic stimulation (TMS) over the left diaphragmatic primary cortex. These observations may seem surprising as they suggest that both anodal and cathodal transcranial DCS decreased the excitability threshold of the corticodiaphragmatic pathway, whereas multiple data in the literature are in favor of cortical neuronal depolarization in the anodal configuration and moderation of neuronal activity at the cortical level in the cathodal configuration [53]. This discrepancy may depend on several factors, such as the distance between the active and reference electrodes, current density reaching the target tissue, or neuronal circuits involved.

A final study in healthy subjects explored the ability of transcranial DCS to modulate the cortical drive to the chest wall muscles, which are involved in voluntary control of expiration as part of phonation (Table 1) [78]. Activity of the internal intercostal and external oblique expiratory muscles was recorded and used to study intermuscular coherence only during expiration. The authors observed that anodal transcranial DCS applied on the motor cortex induced a significant increase in intermuscular coherence of the expiratory muscles during vital capacity expiration, whereas cathodal transcranial DCS had no effect. This work suggests that transcranial DCS, as applied by these authors, can be used to potentiate synchronized force development of the chest wall muscles during voluntary expiration, a possibility that could be of interest as a complement to conventional rehabilitation protocols in patients with neuromuscular deficits that affect voluntary breathing control.

Transcranial DCS application at the cephalic level in a pathophysiological context

A few years after the studies carried out in healthy subjects, the effects of transcranial DCS on ventilatory control were explored in pathophysiological situations according to two

Table 1 Explorations of cortical and spinal DCS effect on breathing in healthy subjects and patients

Study	Participant(s)	Age (years)	Number	Concomitant medication or training	Active and reference electrode positioning	Stimulation parameters	Procedure	Control/sham	Measurements	Breathing observations	Observations other than breathing
Lippold and Redfeam [40]; Redfearn et al. [64]	Healthy subject	Not specified	1	None	Active electrode (cathode) on frontal cortex; reference on right leg (knee)	Transcranial DCS 3 mA, 16 min	Single session	None	Observation of respiratory activity	Decrease in f_R, apnea	Pallor, nausea
Vandermeeren et al. [80]	Healthy subjects	Mean (± SD), 33.8 (± 8.6)	30	None	Active electrode (anode/cathode) on left Fz and reference on right leg	Transcranial DCS 1 mA, 20 min	Single session	Stimulation was stopped after 30 s	f_R, heart rate, blood pressure, R–R interval	No effect on f_R; no analysis of other respiratory variables	No change in autonomic cardiovascular function, heart rate, blood pressure, and sympathovagal balance
Raimundo et al. [61]	Healthy subjects	Mean (range), 30.5 (19–63)	50	None	Active electrode (anode) on C3 (10–20 international system EEG); reference on right supraorbital region	Transcranial DCS 1 mA, 20 min	Single session	Stimulation was stopped after 10 s	Blood pressure, tympanic and hand skin temperature, heart and f_R	No effect on f_R; no analysis of other respiratory variables	No change in autonomic cardiovascular function and thermoregulation
Azabou et al. [7]	Healthy subjects	Mean (range), 27 (22–34)	12	Transmagnetic stimulation (TMS) to elicit diaphragm motor-evoked potentials	Active electrode (anode/cathode) on left diaphragmatic primary motor cortex; reference electrode on right orbit	Transcranial DCS 2 mA, 10 min	3 randomized sessions separated by 10 min: anodal DCS, cathodal DCS and sham	Stimulation lasted 2 min	TMS diaphragm motor-evoked potentials	Decrease in TMS diaphragm motor-evoked potentials induced by both anodal and cathodal transcranial DCS	None

Table 1 (continued)

Study	Participant(s)	Age (years)	Number	Concomitant medication or training	Active and reference electrode positioning	Stimulation parameters	Procedure	Control/sham	Measurements	Breathing observations	Observations other than breathing
Tomczak et al. [78]	Healthy subjects	Mean (range), 34 (18–57)	10	None	Active electrode (anode/cathode) on left motor cortex; reference electrode on right supraorbital region	Transcranial DCS 1 mA, 10 min	3 randomized sessions separated by at least 24 h: anodal DCS, cathodal DCS and sham	Stimulation was stopped after 10 s	Chest wall surface EMG from the right side of the body (over the sixth intercostal space and abdominal oblique regions)	Anodal transcranial DCS increase in intermuscular coherence of expiratory muscles during vital capacity expiration; cathodal transcranial DCS had no effect	None
Lee et al. [38]	Patients with chronic stroke	Transcranial DCS group, mean (± SD) 57.1 (± 13.7); sham group 56.4 (± 14.7)	30	Breathing exercise	Active electrode (anode) on primary motor cortex of damage side (C3, C4; 10–20 international system EEG); reference electrode on contralateral supraorbital region	Not specified	Patients were randomized into either DCS group or sham group; single session	Not specified	Forced vital capacitance and forced expiratory volume at 1 s	Greater transcranial DCS-induced improvement in the forced vital capacitance and forced expiratory volume at 1 s than diaphragmatic breathing exercise alone	None

Table 1 (continued)

Study	Participant(s)	Age (years)	Number	Concomitant medication or training	Active and reference electrode positioning	Stimulation parameters	Procedure	Control/sham	Measurements	Breathing observations	Observations other than breathing
De Carvalho et al. [17]	Patient with high spinal cord injury (C5–C7)	20	1	Respiratory physiotherapy and peripheral electrical stimulation	Active electrode (anode) on supplementary motor area (2 cm anterior to Cz; 10–20 international system EEG) and reference on supraorbital area (FP2; 10–20 international system EEG)	Transcranial DCS 2 mA, 20 min	Over 23 days, one session daily except the weekend, 15 sessions	None	Maximal expiratory pressure, maximal inspiratory pressure, peak cough flow, diaphragmatic mobility and diaphragmatic thickness fraction	Improvement in ventilatory capacities that enabled a decannulation	None

Table 1 (continued)

Study	Participant(s)	Age (years)	Number	Concomitant medication or training	Active and reference electrode positioning	Stimulation parameters	Procedure	Control/sham	Measurements	Breathing observations	Observations other than breathing
Ministro et al. [43]	Patients with resistant hypertension	Mean (±SD), 69 (± 7)	13	Antihypertensive	Active electrode (anode) over primary motor cortex (C3; 10–20 international system EEG); reference over supraorbital area	Transcranial DCS 2 mA, 20 min	DCS or sham randomized sessions separated by 1 week	30 s ramp-up period followed by 30 s ramp-down period	During cardiopulmonary exercise test: f_R, tidal volume, minute ventilation at the peak of exercise, VO_2 peak–peak of oxygen consumption, VE/VCO_2 slope—relationship between minute ventilation and carbon dioxide production, VE/VO_2 slope—relationship between minute ventilation and oxygen consumption, heart rate, systolic and diastolic blood pressure	Improvement of aerobic capacity without any change in f_R and tidal volume	Improvement of cardiac variability during exercise and attenuation of exacerbation of hemodynamic response

Table 1 (continued)

Study	Participant(s)	Age (years)	Number	Concomitant medication or training	Active and reference electrode positioning	Stimulation parameters	Procedure	Control/sham	Measurements	Breathing observations	Observations other than breathing
Andrade et al. [4]	Patients with COVID-19	68.1	56	Inspiratory muscle training program; medication (steroids, antibiotics, adrenergic agent)	Center active electrode (anode) on the left diaphragmatic M1 (4 cm midline and 1 cm anterior to the binaural line); four reference electrodes in a radius around 7.5 cm from the active electrode	High-definition transcranial DCS 3 mA, 30 min	10 consecutive weekdays, 2 sessions per day (morning and afternoon); patients were randomly assigned to DCS or sham group	30 s ramp-up period followed by 30 s ramp-down	Days free from mechanical ventilation, confusion, and organ failure assessments	Transcranial DCS-induced increase in the mean number of days free from mechanical ventilation	Transcranial DCS-induced greater improvement of organs functioning from day 11 of DCS
Chang et al. [12]	Patients with schizophrenia	44.8 ± 10.8	60	Antipsychotic, antihypertensive	Two active electrodes (anodes) over points midway between F3 and Fp1 and F4 and Fp2 (10–20 international system EEG); reference electrodes over bilateral forearms	Bi-anodal transcranial DCS 2 mA, 20 min	2 daily sessions separated by 2 h, 5 consecutive days	30 s of 2 mA stimulation, followed by a 110-μA pulse over 15 ms every 550 ms throughout the remainder of the 20-min period	Heart rate, heart rate variability, blood pressure, f_R	No change in f_R	No change in blood pressure, heart rate and, heart rate variability

Table 1 (continued)

Study	Participant(s)	Age (years)	Number	Concomitant medication or training	Active and reference electrode positioning	Stimulation parameters	Procedure	Control/sham	Measurements	Breathing observations	Observations other than breathing
Niérat et al. [47]	Healthy subjects	Mean (range), 28.3 (21–45)	22	TMS to elicit diaphragm motor-evoked potentials	Active electrode (anode/cathode) on midline of the posterior part of the neck to cover cervical spinal cord segments C3–C5; reference electrode on midline of the anterior part of the neck, just below the cervicomental angle	Transcutaneous spinal DCS 2.5 mA, 15 min	3 randomized sessions separated by at least 3 days: anodal DCS, cathodal DCS and sham	Stimulation was stopped after 90 s	Diaphragm motor-evoked potentials, f_R, tidal volume, ECG, skin conductance	Anodal and cathodal transcutaneous spinal DCS-induced increase in amplitude of diaphragm motor-evoked potentials and cathodal transcutaneous spinal DCS increase in tidal volume	No change in heart rate and skin conductance

distinct objectives, to induce an improvement in a context of impaired breathing and to look for a possible side effect that could affect breathing.

Exploring the value of transcranial DCS for improving ventilation

To date, few studies have investigated use of transcranial DCS as a therapeutic alternative to improve ventilation in pathological contexts where this function is impaired. The reasons for this are undoubtedly both the difficulty of precisely targeting the caudal part of the brainstem (which contains respiratory network that is the origin of the automatic control of ventilation) and also because the voluntary component of ventilation, which has a suprapontine origin, remains insufficiently explored, even though recent work has highlighted its importance in various pathological contexts [19, 30, 58, 76].

Two studies have explored the benefits of using transcranial DCS in the context of nerve tissue damage in stroke and spinal cord injury (SCI; Table 1). Patients suffering from motor-impairing strokes often have impaired ventilation caused by abnormal posture or, more directly by weakened respiratory muscles, and restoration of more efficient ventilation through exercise is a therapy that has developed over the last decade. In this context, Lee and colleagues investigated the possibility that transcranial DCS targeting the primary motor cortex might improve the effect of exercise training on breathing in patients with stroke [38]. Ventilation was explored by measuring forced vital capacity and forced expiratory volume at 1 s, which were more effectively improved by the combination of anodal transcranial DCS with diaphragmatic breathing exercise than diaphragmatic breathing exercise alone. This work opens up interesting perspectives, but it should be noted that the context in which this improvement was observed lacks precision since neither the intensity and duration of stimulation nor the latency between stimulation and ventilatory measurements is specified. In the context of an SCI—a situation in which, as in the case of a stroke, the nerve tissue is damaged—patients may present ventilatory dysfunctions caused by direct damage to cell bodies of the motoneurons innervating respiratory muscles and/or by damage to descending nerve pathways projecting onto these motoneurons, which carry the respiratory rhythmic motor message. When the lesion is high and affects cervical segments of the spinal cord containing phrenic motoneurons that innervate the diaphragm, breathing insufficiency is significant. De Carvalho and collaborators reported the case of a patient with high-level C5–C7 SCI, tracheostomized for 41 days with difficult weaning due to ineffective cough. In this patient, improved respiratory volume and diaphragmatic activity and successful decannulation were achieved after daily repetition of anodal transcranial DCS applied on the supplementary motor area combined with sensory peripheral electrical stimulation (PES) applied on the abdomen and thorax [17]. It should be noted that prior to joint application of transcranial DCS and sensory PES, the patient was receiving respiratory physiotherapy including myotatic stimuli on the abdominal wall, manual therapy to stimulate synchronization of inspiratory muscles, and facilitation of lower rib cage movements and bronchial hygiene maneuvers. However, these procedures were not sufficient to improve the patient's cough and enable effective ventilation. This study therefore reports that combined repeated transcranial DCS and sensory PES in a patient suffering from SCI is not damaging and led to an improvement in breathing. However, in the same study, the authors also described an improvement solely through use of repeated sensory PES in another patient with a T5–T8 lesion. As the authors point out, further studies are therefore needed to corroborate the combination of these two approaches to bring real respiratory benefit to patients.

The value of transcranial DCS has also been investigated in patients with resistant hypertension (RHT), to investigate the possible modulation of ventilatory variability (Table 1) [43]. Although the pathophysiology of RHT remains incomplete, it is accepted that autonomic nervous system dysfunction is involved in its initiation and maintenance. Cardiopulmonary exercise testing (CPET) has been used for many years to diagnose and prognose RHT. The authors observed that anodal transcranial DCS applied on the primary motor cortex improved cardiac variability during exercise. This work also showed that transcranial DCS led to an improvement in aerobic capacity without any change in f_R or tidal volume. Also, it was shown that transcranial DCS as applied during CPET led to both an improvement in aerobic capacity without any change in f_R and tidal volume, and to an attenuation of the exacerbation of the hemodynamic response.

Finally, the therapeutic value of transcranial DCS has also been questioned in the context of COVID-19 in three recent publications [4, 6, 57]. Two of these do not present any results: one describes a clinical study protocol investigating the value of using transcranial DCS to reduce dyspnea in patients with COVID-19 in intensive care units [6], and the other is a literature review focusing on the potential value of transcranial DCS in the management of acute and chronic symptoms of COVID-19 [57]. The third publication presents the results of a randomized clinical trial investigating respiratory rehabilitation using high-definition transcranial DCS (HD-transcranial DCS) in patients with moderate to severe acute respiratory distress syndrome due to COVID-19 (Table 1) [4]. Anodal HD-transcranial DCS targeting the left diaphragmatic motor cortex was applied concurrently with pulmonary rehabilitation. The main result of this study was that the mean number of days without mechanical ventilation during the first 28 days was greater in patients who received

HD-transcranial DCS sessions than in sham patients. This finding suggested a clinically meaningful benefit for HD-transcranial DCS in these patients. As discussed by the authors, this benefit could be due to the restoration of correct excitability of the diaphragmatic primary motor cortex and/or a neuroprotective effect in this brain region owing to an enhancement of cerebral blood flow. Each of these could increase the efficiency of the cortical component of ventilation. This work therefore suggests that HD-transcranial DCS coupled with pulmonary rehabilitation can be considered for intensive care unit patients.

A possible ventilatory effect of transcranial DCS used in treatments unrelated to this function

Exploring possible repercussions of a transcranial DCS application for breathing is of major clinical interest, as this autonomic function, along with others, ensures homeostasis. Any modification of the ventilatory drive linked to neuromodulation of the respiratory network located in the brainstem, by secondary diffusion of the electric field applied at the cortical level, is likely to lead to significant disturbances in breathing. However, to our knowledge, this has been evaluated in only one study. Chang and collaborators investigated whether a bi-anodal transcranial DCS configuration over the prefrontal cortex with extra-encephalic reference placement, effective in improving disorders of patients with schizophrenia, could lead to modulation of certain functions, including breathing. Their objective was to determine whether such an effect could constitute a biomarker for a treatment response (Table 1) [12]. With such a configuration, the possibility of stimulation generating a significant current density in the brainstem was conceivable, and with it a modulation of functions controlled by this part of the brain, including breathing. In such a condition, the authors observed no change in f_R.

DCS application to the spinal cord in healthy subjects

To evaluate the effect on breathing of DCS at the spinal cord level, we carried out a study in healthy subjects to explore the consequences of applying a single session of transcutaneous spinal DCS at the cervical level on ventilatory drive (Table 1) [47]. Anodal and cathodal transcutaneous spinal DCS were delivered to the cervical region and the effect of these stimulations on diaphragm motor-evoked potentials (DiMEPs; electromyography of the diaphragm with surface electrodes) and spontaneous ventilation (plethysmography) were explored. DiMEPs were triggered by application of a TMS near or above the vertex at the end of expiration, when phrenic motoneurons were not activated through automatic ventilatory drive from the brainstem or were inhibited by brainstem inputs; coil positioning was adjusted for each subject to obtain the largest DiMEPs. Once the location had been determined, TMS stimulation was set to generate a DiMEP at 50% of the observable maximum. It is important to note that evoking DiMEPs at this precise moment in the ventilatory cycle enabled exploration of cortical ventilatory drive without interference from the automatic ventilatory drive emanating from brainstem. This work revealed that both anodal and cathodal cervical transcutaneous spinal DCS increased amplitude of DiMEPs and that only cathodal transcutaneous spinal DCS led to an increase in spontaneous tidal volume with no change in spontaneous f_R. These observations led to the hypothesis that the stimulatory effect of cervical transcutaneous spinal DCS depended on an effect at the level of phrenic motoneurons, but not at the level of the brainstem respiratory network. The latter would have led, in parallel to an effect on tidal volume, to a modulation of f_R by modification of activity of respiratory rhythm generators. Thus, cervical transcutaneous spinal DCS, by modulating either the level of excitability of motoneurons or neurotransmission at their level, would make them more apt to be stimulated when receiving the descending respiratory command. The observation of such an effect of cathodal transcutaneous spinal DCS both in terms of DiMEPs amplitude and spontaneous tidal volume is in line with data obtained in recent years, which have suggested that this configuration produces stimulatory effects in the spinal cord [1, 15, 82]. Thus, cathodal transcutaneous spinal DCS would be effective in facilitating the passage not only of voluntary ventilatory control originating in the motor cortex but also of automatic ventilatory control emerging from the brainstem. This possibility is of particular interest as it suggests that cervical cathodal transcutaneous spinal DCS could be used to increase ventilation in pathological situations where the ventilatory drive delivered to respiratory muscles is not sufficient. Finally, to conclude on the interest of applying transcutaneous spinal DCS to the cervical region of the spinal cord to modulate breathing, Fernandes and collaborators modelled the electric field generated in our 2014 study [22]. Their work suggests that, in addition to logically affecting C3–C5 segments of the spinal cord, cervical transcutaneous spinal DCS would cause an electric field to diffuse into the brainstem. Such diffusion would be likely to lead to modulation of the brainstem respiratory network. These data suggest a possible effect of cervical transcutaneous spinal DCS not only on tidal volume, as observed in our study [47], but also on f_R. Future investigations are needed to explore this possibility under physiological conditions different from those we have already explored in healthy

subjects, or under pathophysiological conditions yet to be determined.

Conclusions

DCS is a tool that displays a range of potential uses regarding patient rehabilitation. Studies of the effects of DCS on breathing are scarce but those that are available show promise for future uses of this therapeutic tool. The use of DCS to rehabilitate or stimulate breathing is important in many situations where ventilation is inadequate, and where insufficient therapies are available to clinicians. As it is not easy to explore the effects of DCS on ventilation in patients and healthy subjects, especially as the respiratory neural network responsible for automatic control is located in the caudal part of the brainstem, pilot studies in preclinical models are needed to assess the feasibility of such procedures and to optimize the approach, as well as to decrypt cellular and molecular mechanisms involved in respiratory effects.

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Declarations

Conflict of interest The authors have no financial or proprietary interests in any material discussed in this article.

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