Anodal transcranial direct current stimulation over the right primary somatosensory cortex increases cough reflex sensitivity: a pilot randomised controlled crossover trial

Liya Guo [1], Chunwei Wu[1], Chen Chen[1], Bo Zhang[1], Jian Wu[1], Ying Xie[1,2] and Peijun Gui [1,2]

[1]Department of Rehabilitation Medicine, Beijing Friendship Hospital, Capital Medical University, Beijing, China. [2]Y. Xie and P. Gui contributed equally to this article as lead authors and supervised the work.

Corresponding author: Peijun Gui (guipeijun@hotmail.com)

Shareable abstract (@ERSpublications)
Anodal tDCS stimulation of right primary somatosensory cortex decreases cough reflex threshold, accompanied by an increase in urge-to-cough sensitivity https://bit.ly/3sgL3An

Cite this article as: Guo L, Wu C, Chen C, *et al*. Anodal transcranial direct current stimulation over the right primary somatosensory cortex increases cough reflex sensitivity: a pilot randomised controlled crossover trial. *ERJ Open Res* 2023; 9: 00238-2023 [DOI: 10.1183/23120541.00238-2023].

Received: 17 April 2023
Accepted: 15 Aug 2023

Abstract

Background The cough reflex is a protective reflex of the human body. Increases or decreases in cough reflex sensitivity may be related to chronic cough, aspiration pneumonia and other diseases. The right primary somatosensory cortex (RS1) is the main activation centre for the urge to cough. Here, we discuss the effects of transcranial direct current stimulation (tDCS) of RS1 on the cough reflex and urge to cough. In addition, we explored the role of the left dorsolateral prefrontal cortex (lDLPFC) in cough using tDCS.

Methods 24 healthy young adults completed this pilot randomised controlled crossover experiment. Each person was tested three times, receiving, in random order, anodal tDCS of RS1 or lDLPFC or sham stimulation. The current intensity was set to 2 mA, the stimulation time was 30 min and the interval between any two stimuli was ⩾1 week. After each intervention, the citric acid cough challenge test was used immediately to assess the urge to cough and cough reflex sensitivity.

Results The cough reflex thresholds, expressed as $LogC_2$ and $LogC_5$, were significantly reduced after RS1 anodal stimulation compared to sham stimulation, accompanied by increased urge-to-cough sensitivity (urge-to-cough log–log slope 1.19±0.40 point·L·g^{-1} *versus* 0.92±0.33 point·L·g^{-1}, p=0.001), but the threshold for the urge to cough did not change significantly. There were no significant changes in the urge to cough and cough reflex sensitivity after tDCS anodal lDLPFC stimulation.

Conclusion Anodal tDCS stimulation of the RS1 can increase urge-to-cough sensitivity and reduce cough reflex threshold. The effects of tDCS on cough reflex, as well as the underlying mechanisms driving those effects, should be explored further.

Introduction

The cough reflex, a protective reflex that acts against airway irritation, plays an essential role in the treatment and prevention of respiratory diseases [1]. When the sensitivity of the cough reflex is weakened, the risk of aspiration is increased, which can then lead to aspiration pneumonia [2], especially in elderly and stroke patients. Conversely, when the sensitivity of the cough reflex is enhanced, the body is more sensitive to external stimuli, making patients more prone to chronic refractory cough [3]. These contrasting functions and consequences highlight the importance of keeping cough reflex sensitivity in balance.

The medulla oblongata is believed to be the regulatory centre of the cough reflex [4]. Recent studies have found that a feeling of needing to cough, also called the urge to cough, precedes cough [5]. The urge to cough is a sensory experience associated with airway irritants [6], which also mediates cognitive responses to cough stimulation and is an integral part of the brain's motivational system. The urge to cough increases with cough irritation, and there is also a correlation between the cough intensity and urge to cough [7]. Patients with dementia with Lewy bodies and aspiration pneumonia both have decreased sensitivity of the

cough reflex and urge to cough [8, 9], suggesting that the urge to cough from the cerebral cortex may be important in regulation of the cough reflex. Mazzone and co-workers [10–12] found that when the urge to cough is stimulated by a tussive agent such as capsaicin; functional magnetic resonance imaging (fMRI) showed activation of the supramedullary regions, including the primary sensory cortex, supplementary motor areas, insular cortex, and so on. Farrell *et al*. [13] reported that different brain regions might be involved in different aspects of the stimulus response of the urge to cough. These studies further demonstrate that higher centres play an important role in initiating and suppressing coughs. However, there are few studies on the cortical regulation of the cough reflex.

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that modulates cortical excitability by applying a weak direct current to the scalp with anodal or cathodal stimulation [14]. Anodal tDCS stimulation can induce neuronal depolarisation, thus improving the excitability of the cortical neurons, while cathodal tDCS stimulation exerts precisely the opposite effect. We previously reported that applying anodal tDCS in the right dorsolateral prefrontal cortex (rDLPFC) significantly increased the cough reflex threshold, accompanied by the increase of the urge-to-cough threshold. At the same time, cathodal tDCS stimulation of rDLPFC had no significant effect on the cough reflex [15]. Whether other central intervention targets regulate the cough reflex in a similar manner is not yet known.

Here, we continue to explore the effects of tDCS of different brain regions on cough reflex and the urge to cough. Mazzone *et al*. [11] found that the signals related to the urge to cough were mainly concentrated in the bilateral primary somatosensory cortices. Farrell *et al*. [16] used a neural network localised by the region corresponding to the voxel with the highest level in voxel clusters activated by the inhalation of capsaicin and found that the peak value of somatosensory cortex activation was located in the right hemisphere. Thus, it follows that the right primary somatosensory cortex (RS1) may play a significant part in activating the urge to cough.

In this study, we used tDCS over RS1 in order to explore any effects on the cough reflex and urge to cough in healthy young people. In addition, in previous experiments [15], we have discussed the effects on the cough reflex and urge to cough of tDCS over rDLPFC. It is unclear whether tDCS anodal stimulation of the left dorsolateral prefrontal cortex (lDLPFC) has the same impact. Thus, in addition, we further explored the effects of tDCS over lDLPFC on the cough reflex and urge to cough here.

We hypothesised that tDCS anodal stimulation over RS1 would reduce cough reflex threshold and increase urge-to-cough sensitivity. Anodal tDCS stimulation of lDLPFC would increase cough reflex threshold and attenuate urge-to-cough sensitivity.

Methods

Design

A pilot single-centre randomised controlled crossover trial (www.chictr.org.cn, registration number ChiCTR2100045618) of anodal tDCS stimulation of RS1, lDLPFC *versus* sham condition in healthy young participants (figure 1).

Participants

The study participants were postgraduate students from the Beijing Friendship Hospital at Capital Medical University (Beijing, China). A total of 24 healthy young participants were recruited through WeChat, including four males and 20 females. All subjects were nonsmokers, had no history of respiratory diseases and had no acute upper respiratory infections or seasonal allergic symptoms in the 4 weeks leading up to the study. Exclusion criteria for this study included participants with a history of neuropsychiatric disorders, metal implants, drug or alcohol addiction and participants who were taking any drugs known to affect cough reflex sensitivity. Female participants who were actively menstruating, pregnant or breastfeeding were also excluded. The study protocol was approved by the review board of the Beijing Friendship Hospital medical ethics committee (approval number 2021-P2–014-02), and underwent Chinese clinical trial registration (registration number ChiCTR2100045618).

Citric acid cough challenge test

The citric acid cough challenge test [8, 15] was used to assess cough reflex and the urge to cough. Citric acid was dissolved in 0.9% saline with an initial concentration of 0.7 $g \cdot L^{-1}$ and multiplied to a maximum concentration of 360 $g \cdot L^{-1}$. The citric acid solution was atomised using an ultrasonic nebuliser (NE-C900; Omron Medical Devices, Beijing, China) which produced particles with a median diameter of 3.0±1.0 µm and had an output rate of 0.25 $mL \cdot min^{-1}$. The subjects first inhaled a control solution of saline and then successively inhaled increasing concentrations of citric acid solution. Each citric acid inhalation duration

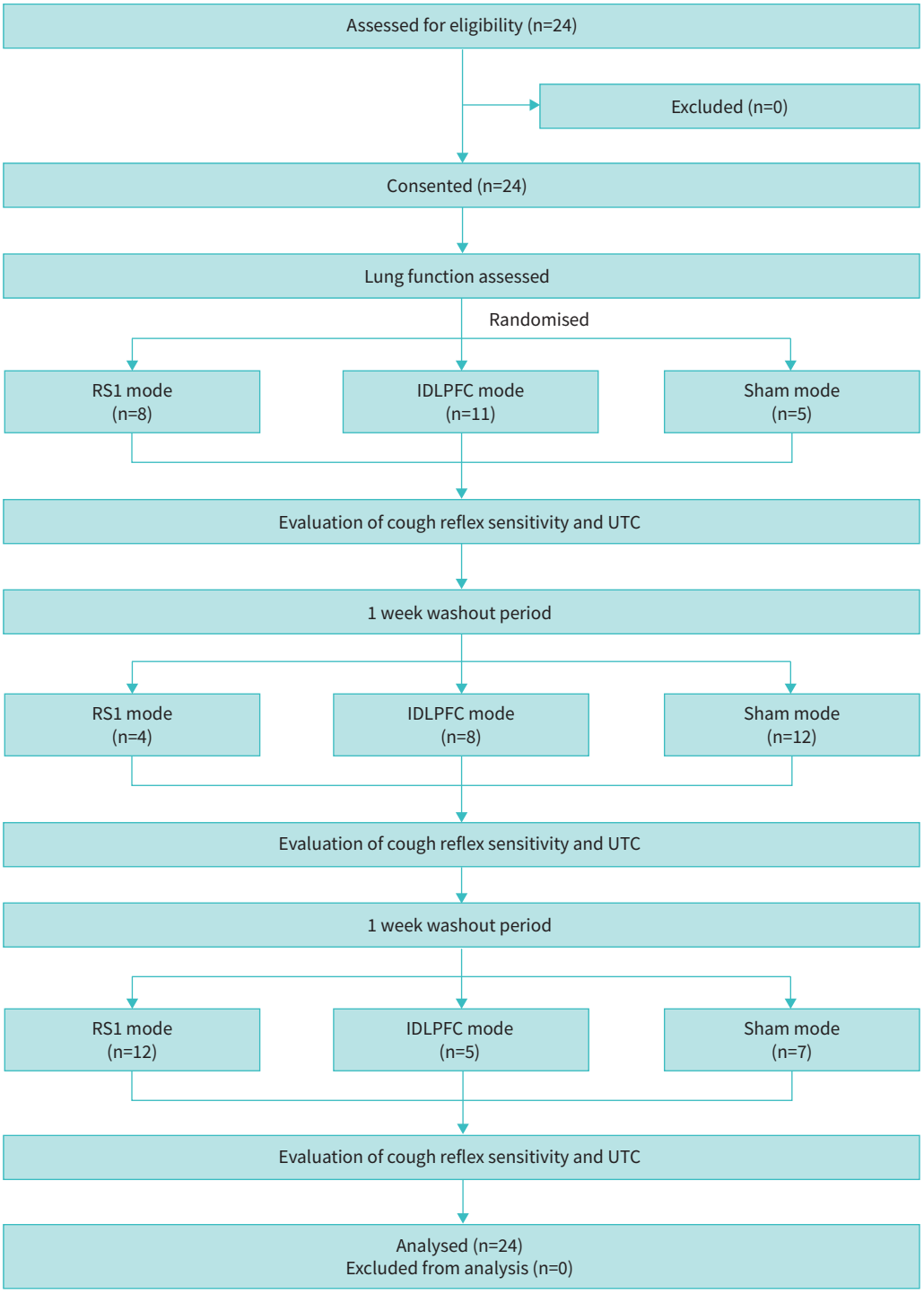

FIGURE 1 Flow diagram describing the study protocol. RS1: right primary somatosensory cortex; lDLPFC: left dorsolateral prefrontal cortex; UTC: urge to cough.

was 1 min with tidal breathing by mouth (wearing a nose clip), and the interval between two sequential inhalations was 2 min. The citric acid inhalation was continued until five or more coughs were elicited. The number of coughs after inhalation of the citric acid solution was counted by technicians who were not informed about the purpose and details of the experiment. The minimum citric acid concentration for eliciting two or more coughs (C_2) and the minimum citric acid concentration for eliciting five or more

coughs (C_5) were defined as the two cough reflex thresholds. The maximum concentration of citric acid that did not cause a cough was recorded as C_{0max}.

After each inhalation, the urge to cough was immediately evaluated using the modified Borg scale. The Borg scale ranges from "no need to cough" (0) to "maximum urge to cough" (10) [9]. During the assessment, we placed the Borg scale in front of participants, and recorded their responses after they were asked to specify the scale score based on their feelings. To assess the intensity of the urge to cough, subjects were asked to ignore other sensations, such as asphyxia, dyspnoea and burning in the throat. Participants were told that their urge to cough could increase, decrease or remain unchanged as they inhaled the atomised citric acid solution and that their Borg scores should reflect this change. There is a linear relationship between the urge-to-cough rating and the corresponding citric acid concentration after log–log transformation, as reported in previous studies [5]. Therefore, each participants' Borg score and the relevant citric acid concentration were log–log transformed in our study. The slope was determined using linear regression analysis and denoted as urge-to-cough log–log slope. The citric acid concentration corresponding to the first Borg scale score that was higher than 0 was recorded as the urge-to-cough threshold (C_u).

Transcranial direct current stimulation

We used the tDCS therapy apparatus produced by Sichuan Zhineng Co. Ltd (Sichuan, China). A pair of electrodes (5×7 cm^2) was used to generate direct current, and stimulation was performed with a constant current of 2 mA (0.057 $mA \cdot cm^{-2}$) for 30 min [15, 17–19]. A pad of the same size as the electrode was placed under each electrode and soaked with 0.9% saline to increase conductivity.

Three different stimulation modes were set in this experiment. Mode 1 (RS1 stimulation) involved placing the anode at RS1 and the cathode at the left shoulder. Mode 2 (lDLPFC stimulation) involved placing the anode at the lDLPFC and the cathode at the right shoulder. Mode 3 (sham stimulation) involved randomly placing the anode at either RS1 or lDLPFC and the cathode at the opposite shoulder. The current intensity was increased progressively in the initial 15 s, then weakened in the subsequent 15 s, and was not energised for the rest of the time. Based on the literature, the activated primary somatosensory cortices related to the urge to cough probably corresponds to Brodmann area 43, located at the caudal limits of the central sulci, near the junction with the lateral fissures [11, 16]. Hence, in our study, following the distribution position of 10–20 electroencephalogram system 64-lead electrode, the RS1 was located between FT8 and C6, at the intersection of the lateral fissure (the junction of the posterior 1/4 of the sagittal line with the outer canthus) and the condylar line (the vertical line through the mandible) (figure 2). The lDLPFC was located in F3, which is 8 cm forward along the sagittal line from the top centre, and then 6 cm outward along the straight line perpendicular to the sagittal line from there (figure 2).

Experimental protocol

Before the experiment began, the experimenter introduced the procedure to the participants. First, lung function was assessed, and personal information was collected for each participant. Then, tDCS stimulation

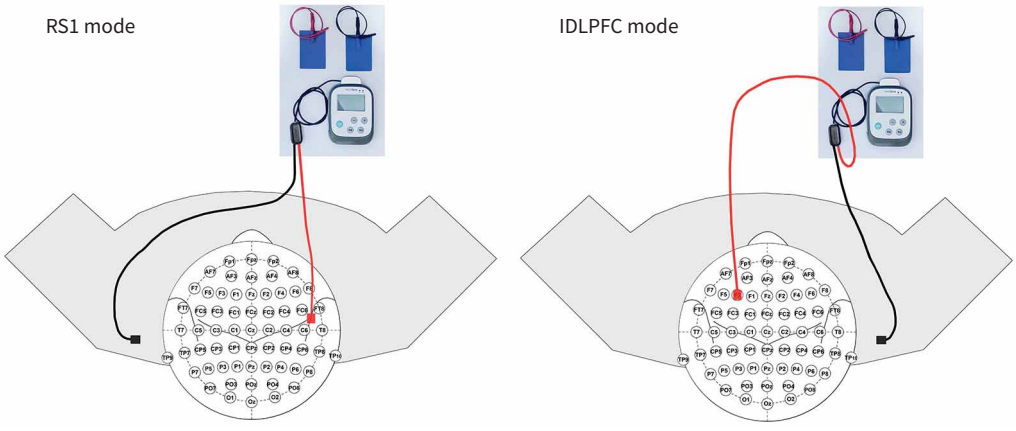

FIGURE 2 Transcranial direct current stimulation electrode position. Anodal electrode placement for the right primary somatosensory cortex (RS1) stimulation was between FT8 and C6. Anodal electrode placement for left dorsolateral prefrontal cortex (lDLPFC) stimulation was in F3.

was performed using the three different intervention modes (mode 1 (RS1 mode), mode 2 (lDLPFC mode) and mode 3 (sham mode)) in an order that was randomised for each participant. After each tDCS intervention, subjects' cough reflex and urge to cough were assessed with the citric acid cough challenge test. The primary outcome was cough reflex threshold (C_5). The secondary outcomes included C_2, C_{0max}, urge-to-cough log–log slope and $C_{u.}$ To avoid persistent tDCS effects, there was at least a 1-week interval between each stimulation. We recorded possible adverse reactions to tDCS by asking participants if they had any discomfort, including dizziness, headaches, neck pain or scalp burning, at the end of each intervention.

Sample size

The sample size was calculated by PASS 11 software. First, a pilot trial with five subjects was conducted. Then, the sample size was calculated using $LogC_5$ at RS1 and sham modes. The required sample size based on a two-sided test (with α=0.05 and a power of 0.8) was 18 participants. Considering study variability and a possible dropout rate of 10%, we set the optimal sample size at 23, and eventually included a total of 24 participants.

Randomisation

The tDCS stimulation order was randomised. Three different intervention modes (mode 1 (RS1 mode), mode 2 (lDLPFC mode) and mode 3 (sham mode)) could generate six intervention sequences: 1-2-3, 1-3-2, 2-1-3, 2-3-1, 3-1-2 and 3-2-1. All subjects were randomly selected for one of six sequences using sampling with replacement. The washout period was ⩾1 week interval between each stimulation.

Blinding

This was a single-blind study. All participants were not informed of which mode they underwent beforehand or afterwards.

Data analysis

Except in certain cases, measurement data are presented as mean±SD. The Shapiro–Wilk normality test was used to assess the normality of the distribution of differences between variables. With the exception of the $LogC_u$ difference between the RS1 and sham stimulation, the $LogC_u$ difference between lDLPFC and sham stimulation, and the urge-to-cough log–log slope difference between RS1 and sham stimulation modes, data were not normally distributed. Paired t-tests was used for data with continuous normal distributions, and Wilcoxon tests were used for data with skewed distributions. All tests were two-sided, and p-values <0.05 were considered statistically significant.

Results

24 subjects were included in this study, including four males and 20 females. The baseline characteristics of participants are shown in table 1. All participants completed three tDCS stimulation trials, and no adverse reactions, such as headaches or scalp burning, were observed during the experiment.

Anodal stimulation of RS1 and sham stimulation

Figure 3 shows the cough reflex thresholds after anodal stimulation of RS1 and sham stimulation, including $LogC_2$ and $LogC_5$. As shown in figure 3a, the average $LogC_2$ after RS1 anodal stimulation was significantly lower than in the sham stimulation (1.32±0.27 $g{\cdot}L^{-1}$ *versus* 1.47±0.32 $g{\cdot}L^{-1}$, p=0.017). Figure 3b shows that the average $LogC_5$ after RS1 anodal stimulation was significantly lower than after

TABLE 1 Baseline characteristics of participants

Participants	24
Age years	24.5±3.05
Male/female	4/20
Right-/left-handed	22/2
Height cm	167.63±7.42
Weight kg	60.5±10.83
FEV_1 L	3.49±0.60
FEV_1 % predicted	102.42±10.94
FVC L	3.86±0.76
FVC % predicted	113.20±15.66
FEV_1/FVC %	91.08±5.52

Data are presented as n or mean±SD. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

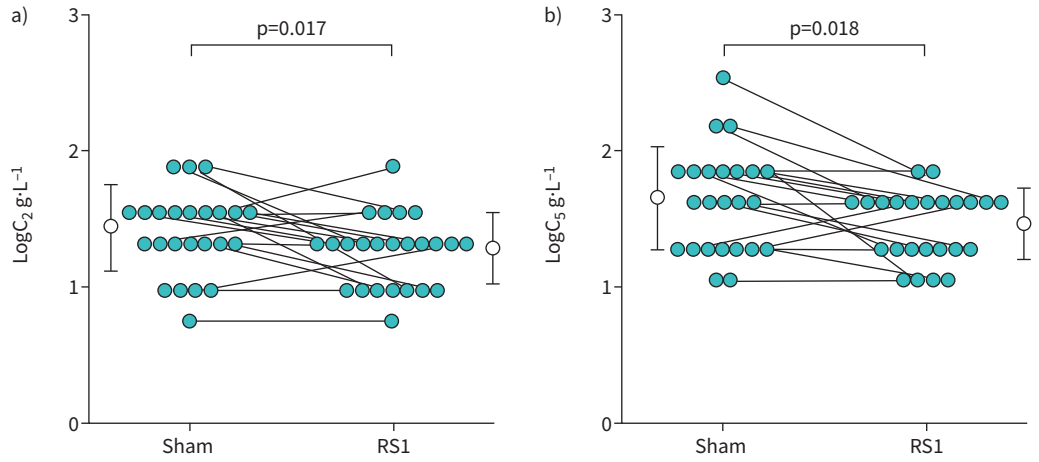

FIGURE 3 Comparison of cough reflex threshold between the anodal stimulation of the right primary somatosensory cortex (RS1) and sham stimulation. a) The log transformation of the lowest concentration of citric acid that elicited two or more coughs ($LogC_2$) in each stimulation; b) the log transformation of the lowest concentration of citric acid that elicited five or more coughs ($LogC_5$) in each stimulation. Closed circles represent the value of each subject; error bars with open circles indicate the mean±SD of the two stimuli.

sham stimulation (1.49±0.27 g·L^{-1} *versus* 1.69±0.39 g·L^{-1}, p=0.018). Figure 4 shows the urge to cough of the sham and lDLPFC stimulation. Figure 4a shows that the urge-to-cough threshold (expressed as $LogC_u$ after RS1 stimulation) did not decrease significantly compared to the sham stimulation (0.42±0.34 g·L^{-1} *versus* 0.40±0.46 g·L^{-1}, p>0.05). However, there were significant differences in $LogC_{0max}$ (0.90±0.34 g·L^{-1} *versus* 1.06±0.33 g·L^{-1}, p=0.025; figure 4b). In addition, we found that the urge-to-cough log–log slope increased significantly after RS1 stimulation compared with sham stimulation, as shown in figure 4c (1.19±0.40 point·L·g^{-1} *versus* 0.92±0.33 point·L·g^{-1}, p=0.001). This means that the urge to cough becomes more sensitive following RS1 stimulation.

Figure 5 shows dose–response relationships between citric acid concentration and the number of coughs (figure 5a) or urge to cough (figure 5b) in individual subjects. The curves for the number of coughs and urge-to-cough Borg ratings after RS1 anodal stimulation are steeper than sham stimulation. It further supported that the urge-to-cough becomes more sensitive following RS1 stimulation. Whether significant differences exist in the urge-to-cough levels elicited at the same citric acid concentrations for both RS1 and sham stimulation needs to be clarified.

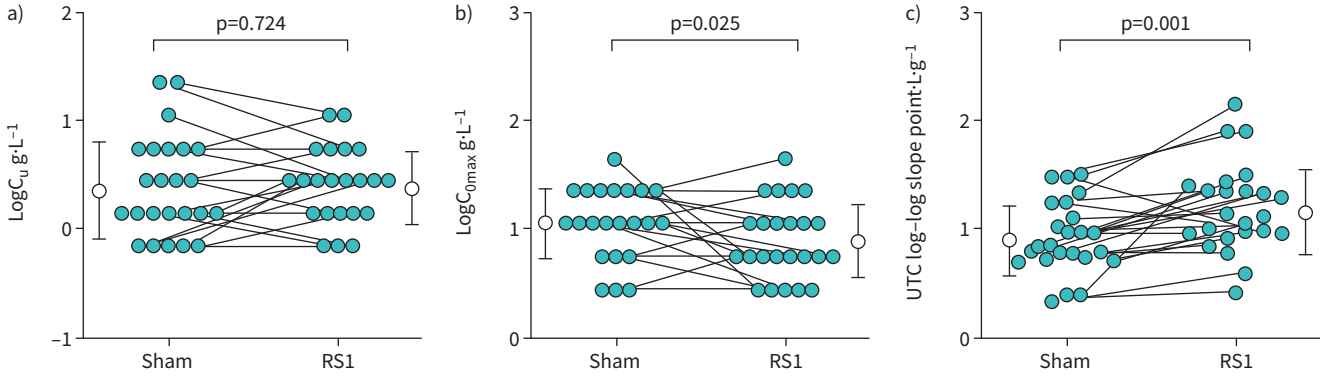

FIGURE 4 Comparison of urge to cough (UTC) between the anodal stimulation of the right primary somatosensory cortex (RS1) and sham stimulation. a) The log transformation of the concentration of citric acid at a threshold of UTC ($LogC_u$) in each stimulation; b) the log transformation of the maximum concentration of citric acid without causing a cough ($LogC_{0max}$) in each stimulation; c) the slope between UTC scores and citric acid concentration on a log–log scale in each stimulation. Closed circles represent the value of each subject; error bars with open circles indicate the mean±SD of the two stimuli.

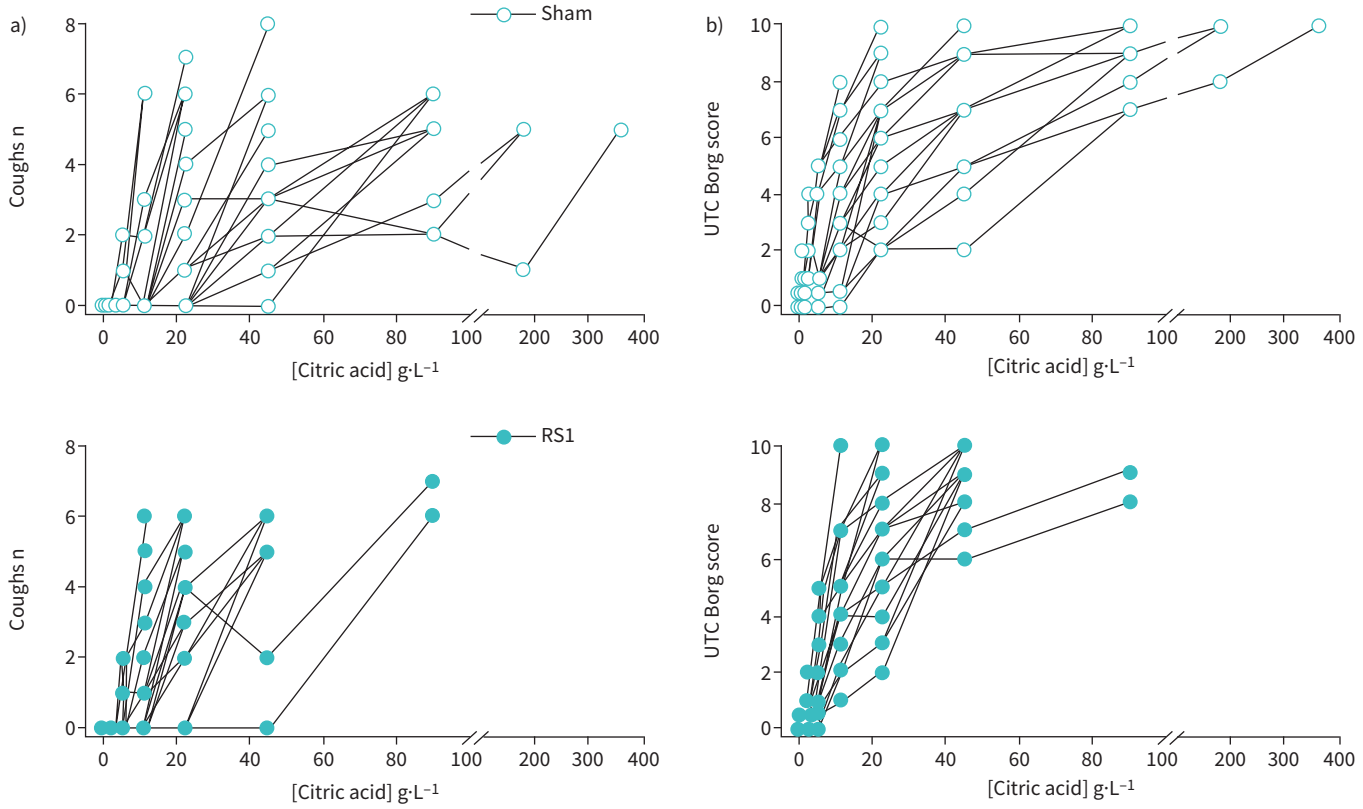

FIGURE 5 Dose–response relationships of citric acid cough challenge test between the anodal stimulation of the right primary somatosensory cortex (RS1) and sham stimulation. a) The number of coughs in each subject; b) Borg scores of urge to cough (UTC) in each subject. In each subject, we stopped the cough challenge test when he or she coughed five or more times.

As shown in figure 6a, the urge-to-cough Borg score at C_u after RS1 anodal stimulation was significantly higher than sham stimulation under the citric acid concentration of C_u of RS1 stimulation (0.81±0.99 *versus* 0.54±0.86, p=0.035). Meanwhile, the urge-to-cough Borg score at C_5 after RS1 anodal stimulation was significantly higher than sham stimulation under the citric acid concentration of C_5 of RS1 stimulation (8.63±1.17 *versus* 7.27±1.83, p=0.012; figure 6c). However, there were no significant differences between the urge-to-cough Borg score at C_2 after RS1 anodal stimulation and sham stimulation under the citric acid concentration of C_2 of RS1 stimulation (7.00±2.25 *versus* 6.33±2.39, p=0.162; figure 6b). Additionally, there were no significant differences between the urge-to-cough Borg score at C_{0max} after RS1 anodal stimulation and sham stimulation under the citric acid concentration of C_{0max} of RS1 stimulation (data not shown).

Anodal stimulation of lDLPFC and sham stimulation

Different results were obtained by anodal stimulation of lDLPFC. Figure 7 shows the cough reflex threshold in the sham stimulation *versus* lDLPFC stimulation. Inspection of figure 7a suggests that there were no significant differences in $LogC_2$ after lDLPFC stimulation compared with sham stimulation (1.42±0.37 $g{\cdot}L^{-1}$ *versus* 1.47±0.32 $g{\cdot}L^{-1}$, p>0.05). Figure 7b shows that there were no significant $LogC_5$ differences between lDLPFC and sham stimulation (1.70±0.34 $g{\cdot}L^{-1}$ *versus* 1.69±0.39 $g{\cdot}L^{-1}$, p>0.05). As shown in figure 8a, there was no significant difference in $LogC_u$ between the two stimulation modes (0.47±0.49 $g{\cdot}L^{-1}$ *versus* 0.40±0.46 $g{\cdot}L^{-1}$, p>0.05). Figure 8b shows that $LogC_{0max}$ did not significantly increase or decrease after lDLPFC stimulation (1.01±0.31 $g{\cdot}L^{-1}$ *versus* 1.06±0.33 $g{\cdot}L^{-1}$, p>0.05). Additionally, no statistically significant differences were found in the urge-to-cough log–log slope after anodal stimulation of lDLPFC compared with sham stimulation (1.05±0.45 $point{\cdot}L{\cdot}g^{-1}$ *versus* 0.92±0.33 $point{\cdot}L{\cdot}g^{-1}$, p>0.05; figure 8c).

Discussion

This study investigated the effects of anodal tDCS stimulation of different cortical regions (including RS1 and lDLPFC) on the urge to cough and cough reflex in healthy young people. In contrast to the sham stimulation, we found that tDCS over RS1 was associated with an apparent increase in urge-to-cough

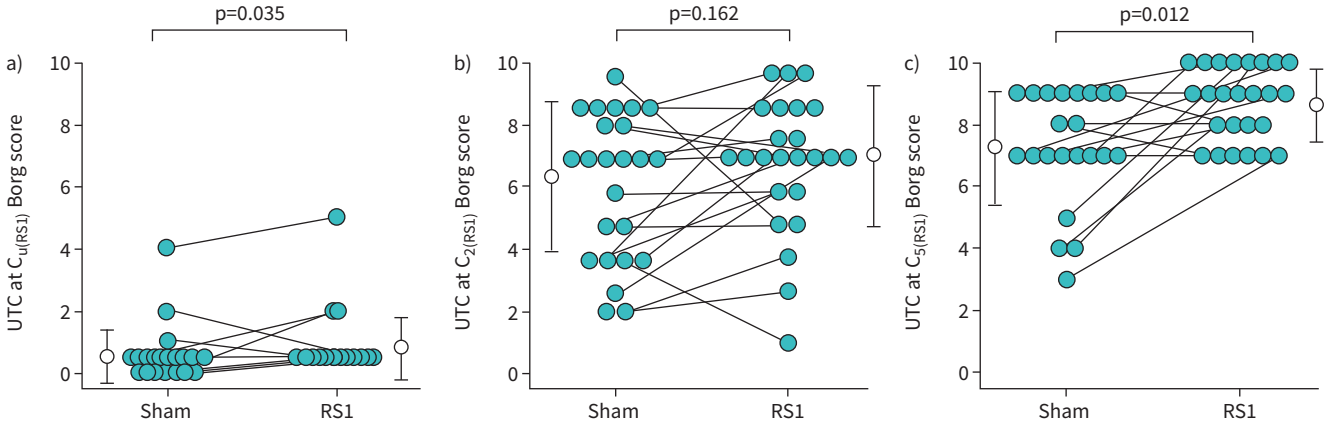

FIGURE 6 Comparison of the urge-to-cough Borg score between the anodal stimulation of the right primary somatosensory cortex (RS1) and sham stimulation. a) The urge-to-cough Borg score at the urge-to-cough threshold (C_u) after RS1 anodal stimulation and sham stimulation under the citric acid concentration of C_u of RS1 stimulation; b) the urge-to-cough Borg score at C_2 (minimum citric acid concentration for eliciting two or more coughs) after RS1 anodal stimulation and sham stimulation under the citric acid concentration of C_2 of RS1 stimulation; c) the urge-to-cough Borg score at C_5 (minimum citric acid concentration for eliciting five or more coughs) after RS1 anodal stimulation and sham stimulation under the citric acid concentration of C_5 of RS1 stimulation. Closed circles represent the value of each subject; error bars with open circles indicate the mean±SD of the two stimuli.

sensitivity and that the cough reflex threshold decreased. However, tDCS application in the lDLPFC did not significantly change the cough reflex threshold or urge to cough.

Several previous studies have explored the central regulatory pathways for coughs and have suggested that the regulation of urge-to-cough-related coughs may depend not only on the brainstem reflex, but also on the integrated activity of the cerebral cortex [20, 21]. The cortex can regulate coughs in several ways, including altering the perception, location and quantification of the afferent stimulus, as well as mediated cognitive and emotional responses to the stimulus [22]. Different brain regions are involved in different aspects of cough regulation. FARRELL *et al.* [16] analysed the functional connectivity of the cough reflex and found that during the inhalation of capsaicin, brain activation was distributed across three distinct cortical subnetworks, including the somatosensory and posterior parietal cortex, which may represent the

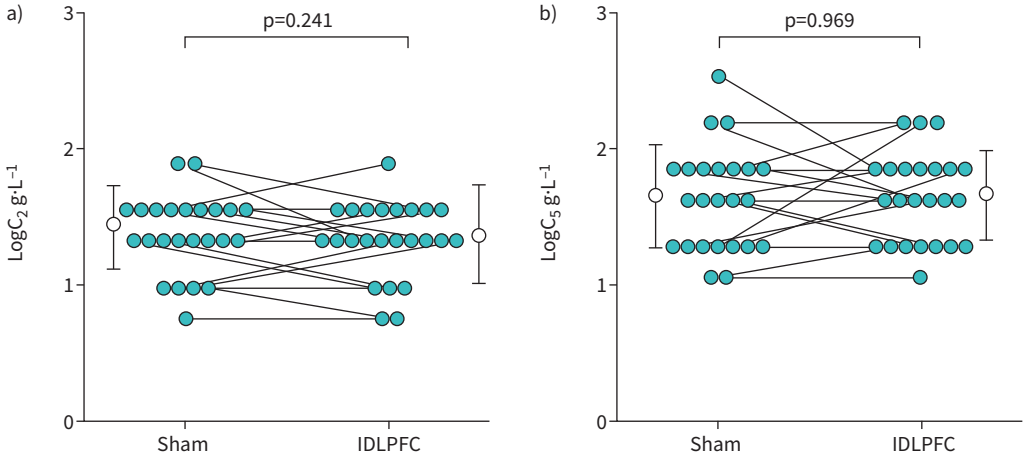

FIGURE 7 Comparison of cough reflex threshold between the anodal stimulation of the left dorsolateral prefrontal cortex (lDLPFC) and sham stimulation. a) The lowest concentration of citric acid that elicited two or more coughs ($LogC_2$) in each stimulation; b) the lowest concentration of citric acid that elicited five or more coughs ($LogC_5$) in each stimulation. Closed circles represent the value of each subject; error bars with open circles indicate the mean±SD of the two stimuli.

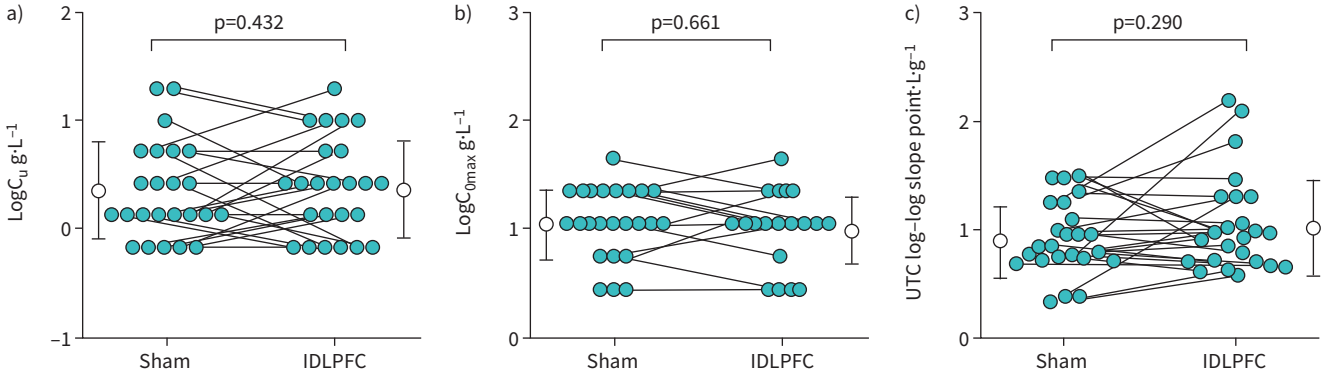

FIGURE 8 Comparison of urge to cough (UTC) between the anodal stimulation of the left dorsolateral prefrontal cortex (lDLPFC) and sham stimulation. a) The log transformation of the citric acid concentration at a threshold of UTC ($LogC_u$) in each stimulation; b) the log transformation of the maximum concentration of citric acid without causing a cough ($LogC_{0max}$) in each stimulation; c) the slope between urge-to-cough scores and citric acid concentration on a log–log scale. Closed circles represent the value of each subject; error bars with open circles indicate the mean±SD of the two stimuli.

perception of the urge to cough. The discovery of the cough central regulation pathway provides the basis for targeting the cerebral cortex as a mediator of the urge to cough and cough reflex.

S1 has sensory functions. fMRI-related studies [11, 13, 16] have found that the region shows its most significant activation in relation to the urge to cough. It has been reported [23] that the sensory components of cough and pain are similar. There is significant overlap between the brain regions associated with airway stimulation and those activated during pain stimulation [24]. Analogies to the neurophysiological mechanisms of pain may help us further understand the central pathways of the urge to cough and cough reflex [25]. A randomised controlled trial [26] investigated the effect of cathodal tDCS stimulation of S1 and the primary motor cortex (M1) on migraines. The results showed that stimulating S1 and M1 significantly reduced the frequency, duration and intensity of migraines. Antal *et al*. [27] used cathodal tDCS to interfere with S1 and explore its influence on acute pain. The results showed that stimulating S1 with cathodal tDCS significantly reduced the perception of pain. Okada *et al*. [28] found that, after pain induction, the expression of N-type voltage-dependent calcium channel subunits in S1 increased, as did the activity and connectivity of neurons in S1. Thus, local blocking of these channels could reduce inflammation-related pain. Taken together, all of these studies suggest that analgesic effects can be produced by regulating S1. Similarly, our results suggest that stimulating the somatosensory cortex may also influence urge-to-cough sensitivity and thus modulate the cough reflex.

The DLPFC is associated with working memory, learning ability, attention and pain. Previous studies [29] have shown that the degree of activation of the rDLPFC is significantly correlated with the antitussive effects of placebos, suggesting that this region plays an important part in suppressing the urge to cough. Our previous experiments [15] further verified that activation of the rDLPFC could suppress the urge to cough and raise the cough reflex threshold. However, the contralateral brain region, the lDLPFC, did not show the same inhibitory effect here. This discrepancy may be related to the different effects of the two cerebral hemispheres. Mylius *et al*. [30] found that the anodal intervention of tDCS in rDLPFC raised heat pain tolerance thresholds (HPTTs), but no significant changes were observed in HPTTs after the tDCS over lDLPFC. They suggested that bilateral DLPFCs may interact with each other or have different functions. Sevel *et al*. [31] explored the structure and sensitivity of DLPFC connections during pain stimulation. They found that DLPFC connections that travel *via* the corpus callosum may affect pain perception. During pain stimulation, the positive feedback between the rDLPFC and lDLPFC increased, and the negative feedback between the lDLPFC and rDLPFC decreased. Overall, these findings support the prominent role of the right cerebral hemisphere in pain processing. Combined with our previous study [15], our results suggest that the rDLPFC may play a more important part in suppressing the cough reflex than lDLPFC.

Impaired cough function is one of the important risk factors for aspiration pneumonia in the elderly. Brain function gradually declines with age. Dysphagia occurs in the early stages of impaired brain function, followed by declines in the ability to perceive the urge to cough, and continues to develop to atussia, the

ultimate cough-related dysfunction. Atussia makes the elderly prone to silent aspiration and recurrent aspiration pneumonia [32]. Antibiotic resistance and the lifestyles of the elderly tend to prolong aspiration pneumonia. Improving urge-to-cough sensitivity may help improve cough reflex function and prevent silent aspiration. The results of this study suggest that tDCS stimulation of the right S1 may enhance the sensitivity of urge to cough, and could potentially be the first step towards developing a new method of preventing aspiration pneumonia in the elderly.

Our study had some limitations. First, most of our subjects were female. There are known sex differences in the cough reflex [33], meaning there could be sex-based differences in the effects of tDCS interventions. Second, we only included healthy young people; our experiments should be repeated in other patient populations, including those with a chronic cough or elderly patients with aspiration pneumonia. Third, there are only two left-handed subjects; the rest are right-handed in this study. Further studies are warranted to clarify whether there is any difference between left-handed and right-handed subjects. In addition, this study only included a single intervention, and the potential sustained effects of multiple tDCS interventions remain unknown. Whether cathodal tDCS stimulation of RS1 modulates the cough reflex and urge to cough needs further elucidation.

Conclusion

Our study showed that anodal tDCS stimulation of the RS1 significantly reduced the cough reflex threshold and increased urge-to-cough sensitivity, but did not change the urge-to-cough threshold. In addition, anodal tDCS stimulation of the lDLPFC had no significant effect on the urge to cough and cough reflex, which may be related to intercortical DLPFC interactions. Future studies should pay close attention to the effects of these targeted interventions on the cough reflex in different types of patients and explore the relevant mechanisms of action to provide new thoughts for the treatment and prevention of related diseases.

Provenance: Submitted article, peer reviewed.

This study is registered at www.chictr.org.cn with identifier number ChiCTR2100045618. The datasets analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate: The study protocol was approved by the review board of the medical ethics committee of Beijing Friendship Hospital affiliated with Capital Medical University (approval number 2021-P2-014-02). All participants signed written informed consent for their participation in this study.

Acknowledgements: We respectfully thank the study participants.

Author contributions: L. Guo: conceptualisation, methodology, investigation, formal analysis and writing (original draft). C. Wu: methodology, investigation and writing (review and editing). C. Chen: methodology, investigation and writing (review and editing). B. Zhang: methodology, investigation and writing (review and editing). J. Wu: methodology, investigation and writing (review and editing). Y. Xie: conceptualisation, methodology, investigation, formal analysis, supervision and writing (review and editing). P. Gui: conceptualisation, methodology, investigation, formal analysis, supervision and writing (original draft, review and editing). All authors read and approved the final manuscript.

Conflict of interest: The authors declare that there is no conflict of interest among the authors and the article's publication will not be affected by individuals' relationships.

Support statement: This study was supported by the National Natural Science Foundation of China (grant number 81800098), Beijing Hospital Authority Youth Program (grant number QML20200109) and Beijing Talents Fund (grant number 2018000021469G204). Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Canning BJ, Chang AB, Bolser DC, *et al.* Anatomy and neurophysiology of cough: CHEST Guideline and Expert Panel report. *Chest* 2014; 146: 1633–1648.
2 Troche MS, Brandimore AE, Okun MS, *et al.* Decreased cough sensitivity and aspiration in Parkinson disease. *Chest* 2014; 146: 1294–1299.
3 Chung KF, McGarvey L, Song WJ, *et al.* Cough hypersensitivity and chronic cough. *Nat Rev Dis Primers* 2022; 8: 45.

4 Mazzone SB, McGarvey L. Mechanisms and rationale for targeted therapies in refractory and unexplained chronic cough. *Clin Pharmacol Ther* 2021; 109: 619–636.
5 Davenport PW, Sapienza CM, Bolser DC. Psychophysical assessment of the urge-to-cough. *Eur Respir Rev* 2002; 12: 249–253.
6 Hilton E, Marsden P, Thurston A, *et al.* Clinical features of the urge-to-cough in patients with chronic cough. *Respir Med* 2015; 109: 701–707.
7 Dicpinigaitis PV, Rhoton WA, Bhat R, *et al.* Investigation of the urge-to-cough sensation in healthy volunteers. *Respirology* 2012; 17: 337–341.
8 Ehibara T, Gui P, Ooyama C, *et al.* Cough reflex sensitivity and urge-to-cough deterioration in dementia with Lewy bodies. *ERJ Open Res* 2020; 6: 00108-2019.
9 Yamanda S, Ebihara S, Ebihara T, *et al.* Impaired urge-to-cough in elderly patients with aspiration pneumonia. *Cough* 2008; 4: 11.
10 Mazzone SB, Cole LJ, Ando A, *et al.* Investigation of the neural control of cough and cough suppression in humans using functional brain imaging. *J Neurosci* 2011; 31: 2948–2958.
11 Mazzone SB, McLennan L, McGovern AE, *et al.* Representation of capsaicin-evoked urge-to-cough in the human brain using functional magnetic resonance imaging. *Am J Respir Crit Care Med* 2007; 176: 327–332.
12 Singh N, Driessen AK, McGovern AE, *et al.* Peripheral and central mechanisms of cough hypersensitivity. *J Thorac Dis* 2020; 12: 5179–5193.
13 Farrell MJ, Cole LJ, Chiapoco D, *et al.* Neural correlates coding stimulus level and perception of capsaicin-evoked urge-to-cough in humans. *Neuroimage* 2012; 61: 1324–1335.
14 Chase HW, Boudewyn MA, Carter CS, *et al.* Transcranial direct current stimulation: a roadmap for research, from mechanism of action to clinical implementation. *Mol Psychiatry* 2020; 25: 397–407.
15 Gui P, Wang L, Guo L, *et al.* Effects of transcranial direct current stimulation on cough reflex and urge-to-cough in healthy young adults. *Respir Res* 2022; 23: 99.
16 Farrell MJ, Koch S, Ando A, *et al.* Functionally connected brain regions in the network activated during capsaicin inhalation. *Hum Brain Mapp* 2014; 35: 5341–5355.
17 Zhang X, Liu B, Li N, *et al.* Transcranial direct current stimulation over prefrontal areas improves psychomotor inhibition state in patients with traumatic brain injury: a pilot study. *Front Neurosci* 2020; 14: 386.
18 Nitsche MA, Cohen LG, Wassermann EM, *et al.* Transcranial direct current stimulation: state of the art 2008. *Brain Stimul* 2008; 1: 206–223.
19 Oveisgharan S, Organji H, Ghorbani A. Enhancement of motor recovery through left dorsolateral prefrontal cortex stimulation after acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2018; 27: 185–191.
20 Mazzone SB, McGovern AE, Yang SK, *et al.* Sensorimotor circuitry involved in the higher brain control of coughing. *Cough* 2013; 9: 7.
21 Ando A, Farrell MJ, Mazzone SB. Cough-related neural processing in the brain: a roadmap for cough dysfunction? *Neurosci Biobehav Rev* 2014; 47: 457–468.
22 Driessen AK, Farrell MJ, Mazzone SB, *et al.* Multiple neural circuits mediating airway sensations: recent advances in the neurobiology of the urge-to-cough. *Respir Physiol Neurobiol* 2016; 226: 115–120.
23 Gracely RH, Undem BJ, Banzett RB. Cough, pain and dyspnoea: similarities and differences. *Pulm Pharmacol Ther* 2007; 20: 433–437.
24 Mazone SB, McGovern AE, Koo K, *et al.* Mapping supramedullary pathways involved in cough using functional brain imaging: comparison with pain. *Pulm Pharmacol Ther* 2009; 22: 90–96.
25 Abubakar AB, Bautista TG, Dimmock MR, *et al.* Behavioral and regional brain responses to inhalation of capsaicin modified by painful conditioning in humans. *Chest* 2021; 159: 1136–1146.
26 Rahimi MD, Fadardi JS, Saeidi M, *et al.* Effectiveness of cathodal tDCS of the primary motor or sensory cortex in migraine: a randomized controlled trial. *Brain Stimul* 2020; 13: 675–682.
27 Antal A, Brepohl N, Poreisz C, *et al.* Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. *Clin J Pain* 2008; 24: 56–63.
28 Okada T, Kato D, Nomura Y, *et al.* Pain induces stable, active microcircuits in the somatosensory cortex that provide a therapeutic target. *Sci Adv* 2021; 7: eabd8261.
29 Leech J, Mazzone SB, Farrell MJ. Brain activity associated with placebo suppression of the urge-to-cough in humans. *Am J Respir Crit Care Med* 2013; 188: 1069–1075.
30 Mylius V, Jung M, Menzler K, *et al.* Effects of transcranial direct current stimulation on pain perception and working memory. *Eur J Pain* 2012; 16: 974–982.
31 Sevel LS, Letzen JE, Staud R, *et al.* Interhemispheric dorsolateral prefrontal cortex connectivity is associated with individual differences in pain sensitivity in healthy controls. *Brain Connect* 2016; 6: 357–364.
32 Ebihara S, Sekiya H, Miyagi M, *et al.* Dysphagia, dystussia, and aspiration pneumonia in elderly people. *J Thorac Dis* 2016; 8: 632–639.
33 Gui P, Ebihara S, Kanezaki M, *et al.* Gender differences in perceptions of urge to cough and dyspnea induced by citric acid in healthy never smokers. *Chest* 2010; 138: 1166–1172.