Applications of transcranial direct current stimulation for understanding brain function

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In recent years there has been an exponential rise in the number of studies employing transcranial direct current stimulation (tDCS) as a means of gaining a systems-level understanding of the cortical substrates underlying behaviour. These advances have allowed inferences to be made regarding the neural operations that shape perception, cognition, and action. Here we summarise how tDCS works, and show how research using this technique is expanding our understanding of the neural basis of cognitive and motor training. We also explain how oscillatory tDCS can elucidate the role of fluctuations in neural activity, in both frequency and phase, in perception, learning, and memory. Finally, we highlight some key methodological issues for tDCS and suggest how these can be addressed.

Introduction to the use of tDCS in neuroscience

tDCS (see Glossary) offers a non-invasive means by which to establish causal relationships between circumscribed regions of the brain and their underlying perceptual, cognitive, and motor functions (Box 1). To date, tDCS has been used to alter performance across a range of cognitive tasks [1,2] (Table 1), and has been trialled as a treatment for a variety of psychiatric and neurological conditions [3,4], including depression [3,5], stroke [4], and altered states of consciousness [6]. Recently there has been debate in the popular media over the use of tDCS to enhance performance and augment gains from cognitive training [7–12]. We argue that tDCS is more than a tool for cognitive enhancement/treatment. Recent developments in our understanding of the neural basis of tDCS [5,13–15] have allowed researchers to make inferences regarding the neural processes underlying specific behaviours, including those tied to learning, memory, perception, and motor actions.

In this review, we provide a summary of the neurobiological effects of tDCS, highlighting polarity-specific modulations of neural excitability and synaptic processes. We discuss some of the important advances that have been made with tDCS in the fields of neural connectivity [16], neural oscillations [17], and cognitive training [18–20]. These advances are generating mechanistic insights into the neural bases of behaviour.

Glossary

Anode: an electrode with a positive charge.
Anodal tDCS: stimulation applied via the anode, typically associated with increased cortical excitability and decreased levels of the neurotransmitter GABA.
Cathodal tDCS: stimulation applied via the cathode, typically associated with decreased cortical excitability and decreased levels of the neurotransmitter glutamate.
Cathode: an electrode with a negative charge.
Electroencephalography (EEG): measurement of electrical activity on the scalp, typically via multiple electrodes. Neural activity is reflected by small changes in electrical potential.
Magnetic resonance spectroscopy (MRS): type of magnetic resonance imaging that allows the non-invasive measurement of metabolites (including neurotransmitters). MRS provides the concentrations of detectable metabolites in the measured area of the brain.
Motor evoked potentials (MEPs): activity in a muscle induced, in this context, by a TMS pulse applied to the primary motor cortex. MEPs are measured via electrodes placed on the skin over the targeted muscle, and are used as a measure of cortico-spinal excitability.
Offline stimulation: stimulation applied at rest, before or after a task is undertaken.
Online stimulation: stimulation applied while a participant undertakes a task.
Oscillatory transcranial direct current stimulation (oscillatory tDCS): a form of tDCS in which the current oscillates at a given frequency.
Plasticity: changes in structural or functional pathways in the brain in response to experience.
Reference electrode: for a single target region in the brain, the second electrode is referred to as the reference. This electrode can be placed over a non-brain region (e.g., the cheek or mastoid) or a brain area thought not to be involved in the relevant process(es). The reference electrode is sometimes referred to as the ‘return’ electrode.
Region of interest (ROI): an area of the cortex targeted with tDCS.
Resting state fMRI (rsfMRI): measurement of the blood oxygen level-dependent (BOLD) signal while a participant is at rest. rsfMRI allows analysis of brain activity and networks in the absence of any specific task.
Sham stimulation: a form of stimulation in which the current duration or intensity are substantially smaller than in active stimulation. Sham stimulation can be thought of as a placebo condition.
Transcranial direct current stimulation (tDCS): non-invasive electrical stimulation of the brain via electrodes placed on the scalp. Typically, a current is ramped up, held constant for a period of time (most commonly 8–15 min), and then ramped down.
Transcranial magnetic stimulation (TMS): non-invasive brain stimulation using a magnetic field to induce an electric current in underlying brain tissue.
TMS evoked potentials: a change in electric potentials measured with EEG in response to a TMS pulse.
Visual evoked potentials (VEPs): a change in electric potentials measured with EEG in response to a visual stimulus or a TMS pulse over visual cortex.
Box 1. Types and uses of transcranial electrical stimulation

There are several types of transcranial electrical stimulation (tES). All typically involve the application of a current via two electrodes, where one or both electrodes are placed on the scalp. The most widely used method of tES is transcranial direct current stimulation (tDCS), where a constant current is passed from one electrode (the anode) to the other (the cathode) over a period of time (usually 8–15 min). Stimulation typically leads to polarity-specific modulations in cortical excitability, and in neurotransmitter and neuromodulator systems in the stimulated cortex (see Neurobiological effects of tDCS). tDCS has been used to examine the neural processes underlying a range of psychological processes, including working memory, language, mathematical cognition, spatial attention, and response selection (Table 1). Recently, tDCS has been shown to modulate high-level processes such as social norm compliance [115]. Clinical applications for several conditions exist, with evidence that tDCS can aid the treatment of stroke [4], depression [3,5], and minimally conscious states [6].

Unlike correlational methods such as functional magnetic resonance imaging (fMRI) (where the BOLD signal is the dependent variable), tDCS can provide causal evidence that a brain region is involved in a behaviour of interest. tDCS offers a perspective that is unique with respect to other brain stimulation methods, such as transcranial magnetic stimulation (TMS). For example, tDCS influences a larger region of the cortex than TMS; it acts as a neural modulator without causing action potentials; it can produce opposing effects through anodal and cathodal stimulation, but with similar peripheral sensations (scapel tingling); it produces fewer physiological artefacts than TMS (e.g., muscle twitches and auditory noise); and it is cheaper, more portable, and easier to apply than TMS. Many of these advantages have led to the increased use of tDCS in clinical and research settings. In particular, the ability of tDCS to provide polarity-specific modulations (without causing action potentials) has provided a unique perspective on the relationship between brain and behaviour.

Two other types of tES are oscillatory tDCS and transcranial alternating current stimulation (tACS). Both oscillatory tDCS and tACS involve the application of a current in which intensity fluctuates at a given frequency. For oscillatory tDCS, these fluctuations remain polarity specific at each electrode. For tACS the current oscillates such that each electrode does not remain polarity specific [116]. Both tACS and oscillatory tDCS allow the specific modulation of neural oscillations, giving causal insights into neural communication.

A final type of tES is transcranial random noise stimulation (tRNS). tRNS involves random fluctuations in current intensity, essentially adding neural ‘noise’ to the targeted region(s). This stimulation type has provided promise in the field of cognitive enhancement [117,118] and as a clinical treatment [119]. The idea of adding neural noise to a system, and finding resulting improvement, may seem counter-intuitive. However, the enhancement of a signal through the addition of noise can be explained via stochastic resonance [120], whereby a weak signal is boosted by an increase in background noise [120].

Neurobiological effects of tDCS

Excitability changes induced by tDCS

Animal studies have shown that anodal stimulation applied directly to the cortex causes the resting membrane potential to become more positive, whereas cathodal stimulation causes hyperpolarisation [21,22]. If stimulation is of sufficient duration, these effects are comparable during and immediately after application [21,22]. Conceptually, one can think of the effects of depolarisation and hyperpolarisation caused by anodal and cathodal tDCS as modulations that make it more or less likely, respectively, that a stimulated neuron will produce an action potential.

When tDCS is applied to the primary motor cortex in humans, anodal stimulation causes increased neural excitability, whereas cathodal stimulation results in decreased excitability (Figure 1), as reflected in motor evoked potentials (MEPs) [23–26] and transcranial magnetic stimulation (TMS) evoked potentials [26]. Comparable modulations by anodal and cathodal tDCS have been reported in the visual cortex, as measured by TMS-induced phosphenes [27] and visual evoked potentials (VEPs) [28]. These modulations are also reflected in changes in the blood oxygen level-dependent (BOLD) signal measured using fMRI [29–31]. Anodal stimulation tends to increase the BOLD signal, whereas cathodal stimulation decreases it [32,33]. It is noteworthy, however, that some researchers have found no change in BOLD within regions of targeted cortex, either during a relevant task (e.g., motor movements following motor cortex stimulation) or at rest [34]. Functionally connected regions distant from the electrode site can also be influenced by tDCS [15,33], including subcortical structures [16,33], and this modulation can be in the same [35] or opposite [34] direction to that predicted from the polarity of stimulation over the target region. Together these findings reveal that the effects of tDCS on brain function are complex, and that stimulation over relatively focal areas of cortex can yield widespread changes across the brain (see ‘Using tDCS to examine connectivity and network communications’).

Factors influencing tDCS-induced excitability changes

tDCS effects on excitability can be modulated by several factors. First, the intensity of stimulation affects excitability. Whereas low-intensity (1 mA) stimulation causes conventional polarity-specific modulation of neural excitability, higher-intensity (2 mA) stimulation can lead to increased excitability from both stimulation polarities [36]. Second, pairing a task with stimulation can modulate motor cortex excitability [37] relative to stimulation delivered at rest. For example, a cognitive task can reverse the typical relationship between polarity of current flow and excitability, whereas a motor task can reduce excitability following both anodal and cathodal stimulation [38]. Third, the reliability of the induced excitability changes can vary both from session to session within individuals, and across participants [37]. Some variability is undoubtedly due to differences in current flow between individuals (Box 2), in addition to potential differences in neurotransmitter efficiencies (see [5]).

Explanations for within-participant variability include individual modulating factors such as intake of neuro-affective substances (e.g., nicotine [39]), and fluctuations that occur over time. For example, time of day is known to influence motor cortex plasticity, as measured with TMS [40]. State-dependent variations in the effect of stimulation have been studied using the combined application of tDCS and TMS. For example, TMS can be used repetitively (rTMS) to induce prolonged changes that cause increased excitability (e.g., with 5 Hz stimulation [41]) or decreased excitability (e.g., with 1 Hz stimulation [42]). If the motor cortex is preconditioned with cathodal stimulation, however, a normally inhibitory rTMS protocol will increase excitability [43], and this interaction can modulate pain thresholds in healthy participants [44]. Similarly, for
<table>
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<td>Bilateral PPC or DLPFC (anode left, cathode right), 3 cm²</td>
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<td>Sandrini et al.</td>
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<tr>
<td>Reis et al.</td>
<td>Left M1, 25 cm²</td>
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Key studies that have demonstrated tDCS modulations of behaviour. We give examples from the domains of attention, language, working memory, mathematical learning, error awareness, and perception. The target electrode size and placement, reference electrode location, stimulation features (parameters, types, and timing), participant sample size, design type, and key findings are given for each study.
visual cortex, the pairing of anodal tDCS and excitatory rTMS will reduce excitability [45]. In addition, the pairing of cathodal tDCS and inhibitory rTMS causes an increase in excitability in the visual cortex [45]. Such modulations of excitability via tDCS highlight the potential for stimulation to interact with the prior state of the cortex, called ‘homeostatic plasticity’ [43] or ‘metaplasticity’ [45].

Because the state of affected neurons prior to stimulation can alter the effect of stimulation on cortical excitability, it follows that modulation of excitability by tDCS might itself be influenced by factors known to affect the state of the cortex (e.g., tasks, practice, fatigue). In this context, tDCS could be utilised to understand how such factors affect the brain. Better understanding of these state-based interactions could be harnessed to optimise the magnitude, and direction, of cortical excitability modulations induced via tDCS.

**Neurotransmitters and modulators**

Animal models suggest that changes in excitability following direct cortical stimulation are likely due to changes in the membrane potential of targeted neurons [21,22]. In humans, drugs that block sodium channels (e.g., carbamazepine) or calcium channels (e.g., flunarizine) reduce or eliminate the normal increase in cortical excitability elicited by anodal stimulation [46]. By contrast, these same drugs have no effect on excitability changes associated with cathodal stimulation [46], presumably because cathodal stimulation causes hyperpolarisation of affected neurons and, consequently, inactivation of sodium and calcium channels [47]. Collectively, these findings suggest tDCS exerts its effects via modulation of neuronal membrane potentials.

Further evidence that tDCS modulates synaptic activity via neurotransmitters has come from human studies using
Several mathematical models have been developed to describe the path of current flow in cortical tissue induced by tDCS [14,106,107,109–111]. These models estimate the pathway based on the electrical conductivity of the tissue that lies between the electrodes. Early approaches used simplified spherical head models to calculate current flow [123], and estimated current distribution based on these assumptions. Newer models have used MRI scans, and have segmented the different tissue types (e.g., skin, skull, CSF, grey matter, and white matter) [110]. After segmentation, separate conductivity values are given to each tissue type, producing a map of conductivity for a realistic, 3D head model. Current distribution is then estimated from these different tissue types [14,110].

As a rule, the strongest current is induced at cortical locations that are nearest the electrodes [110]. Current density generally diminishes with increasing distance from the electrodes [110], but some effects of stimulation can be widespread across the brain [14]. The precise flow of current may be modulated by individual differences in factors such as head size and shape, skull thickness, and ventricle size [14]. These individual differences may be further exaggerated where there are abnormalities in the brain that could alter conductivity, for example, following brain lesions [14]. Recent advances have been made in applying models to individual participants’ anatomy [14]. Such subject-specific modelling is important to fully understand and characterise the effects of stimulation [124]. This recent work on developing realistic head models will allow researchers to determine the optimal placement of electrodes for each individual to maximise the efficacy of stimulation.

**Box 2. Modelling current flow**

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Several drug interventions have linked the neuromodulators serotonin and dopamine to tDCS after-effects [47,52,55–57]. Administration of L-dopa can reverse the typical increase in excitability due to anodal stimulation, and prolong the attenuation of excitability following cathodal stimulation [55,56]. By contrast, a serotonin reuptake inhibitor (citalopram) has been shown to reverse the inhibitory effect of cathodal stimulation, and to enhance and prolong increased excitability following anodal stimulation [57]. Further, genetic polymorphisms linked to serotonin function (5-HTTLPR) predict tDCS treatment outcomes in patients with major depressive disorders [5], suggesting an effect of tDCS on the serotonergic system and highlighting the importance of genetic factors in determining individual responses to tDCS. The cholinergic system may also contribute to tDCS effects. Acetylcholine inhibitors block the influence of anodal stimulation and diminish that of cathodal stimulation [58]. Moreover, administration of nicotine can abolish offline effects of stimulation, further suggesting a link with the cholinergic system [39] and highlighting a potential source of within-participant variability.

To summarise, tDCS can alter GABA [47,48,51,52], glutamate [48,50,52], acetylcholine [39], serotonin [5,57], and dopamine [55,56] systems. These modulations likely affect plasticity processes, making tDCS an important tool for clinical treatment. A rich avenue for future research is how tDCS alters these systems, the consequences of such modulations, and the link between neurotransmitters/modulators and behaviour.

### Using tDCS to examine connectivity and network communication

#### Functional networks

A popular approach for examining functional brain networks involves measuring activity via fMRI while participants are at rest [59]. Such ‘resting state’ scans (rsfMRI) allow measurement of correlated activity across distinct brain regions from which hypotheses regarding functional relationships between these areas can be tested. rsfMRI studies have helped to delineate several large-scale brain networks. The default-mode network [60], includes inferior parietal, medial temporal, and medial prefrontal cortices [61], and shows low-frequency oscillations (~0.1 Hz) that are most active at rest. There is also substantial evidence for networks that are important in cognitive control. These include the fronto-parietal network [62] and the cingulo-opercular network [63].

Several studies have examined the influence of tDCS on resting-state network activity. Anodal stimulation over the left motor cortex increases functional connectivity between the left motor cortex and the ipsilateral thalamus, caudate nucleus, and parietal association cortex [16], whereas cathodal stimulation decreases connectivity between the left motor cortex and the contralateral putamen [16]. Bilateral stimulation of motor cortex induces widespread changes in functional connectivity, in particular with the prefrontal cortex, and the primary and secondary motor cortices [64]. tDCS over prefrontal cortex induces alterations in both the default mode and fronto-parietal networks [65]. Such tDCS-induced changes in the default-mode network have led to the suggestion that increased connectivity results in diminished top-down control and associated cognitive impairment [66].

Combining tDCS and TMS allows the investigation of causal interactions between brain areas. For example, preconditioning the supplementary motor area (SMA) region with anodal stimulation reduces excitability in motor cortex, and increases excitability in somatosensory cortex, whereas cathodal tDCS leads to the opposite pattern [67]. These findings suggest that the SMA region has an inhibitory input to the motor cortex, and an excitatory input to the somatosensory cortex [67]. In another study, Feurra et al. [68] stimulated the parietal cortex with tDCS and measured MEPs while participants imagined moving their fingers. Undertaking this motor imagery task enhanced corticospinal excitability. The effect was larger following ipsilateral anodal stimulation and smaller following ipsilateral cathodal stimulation [68], relative to sham stimulation, suggesting that a parieto-motor circuit is involved in motor imagery [68].

Taken together, these findings suggest that tDCS can cause changes in functional networks across the brain. When paired with neuroimaging, tDCS can be a powerful tool for identifying and describing functional brain.
networks [69]. When paired with TMS, tDCS allows identification of interactions between brain regions. These are crucial advantages of tDCS given the growing consensus that cognition and behaviour reflect the interaction of many regions acting in concert [70,71].

Modulating neural communication

Endogenous oscillations in neural activity provide an important means of communication between distant sites across the brain [72]. For example, slow-wave oscillations between the neocortex and hippocampus during sleep are thought to be important for long-term memory formation [73,74]. There is evidence that conventional anodal or cathodal tDCS can cause changes in oscillatory cortical activity in the theta [75,76], alpha [76], beta [75,77], and gamma [77] ranges. The precise mechanisms by which these changes in oscillations occur remain unclear. However, tDCS can also be used with an oscillatory change in current density to directly manipulate the frequency of neural oscillations [17]. By electrically stimulating a region of cortex to adopt a particular frequency and phase of oscillation, the roles of frequency and phase can be causally examined in relation to behaviour. For example, when dorsolateral prefrontal cortex is stimulated during sleep to induce low-frequency oscillations (0.75 Hz) the retention of memories in rats [78] and humans [73,79,80] is enhanced. Likewise, the same oscillatory tDCS protocol can improve learning of new information during wakefulness [81]. Hence, by inducing slow, phasic changes in cortical excitability, learning and memory can be improved. These findings provide an avenue for enhancing memory in healthy individuals and patient groups, and confirm that slow-wave oscillations in the frontal cortex play a key role in memory processes [75,77].

In-phase oscillations across sensory and parietal cortices have been identified as important factors in perception [82,83]. Neuling et al. (2012) confirmed the importance of in-phase activity by applying 10 Hz oscillatory tDCS to the auditory cortex [84]. When the oscillations were in-phase with an auditory stimulus, detection was improved relative to when oscillations were out of phase with the stimulus [84]. Gamma-frequency oscillations in the occipito-parietal cortex have also been implicated in visual bistable motion perception [85], and tDCS-induced gamma, but not theta, oscillations reduce perceptual switches in motion direction [85]. This reduction presumably reflects ‘blocking’ of changes in frequency that typically trigger shifts in perceived motion direction for bistable stimuli [85].

In short, using tDCS to modulate the frequency and phase of oscillations can provide causal insights into neural communication. The work described above has yielded new insights in the fields of perception [84,85], learning [81], and memory [73,79,80]. Oscillatory tDCS also has the capacity to act as a cognitive enhancer, which may in turn lead to new treatments for clinical conditions characterised by learning and memory impairments.

Cognitive and motor training

tDCS can enhance performance across a range of cognitive tasks [1,2,86]. Indeed, there has been considerable discussion around the use of tDCS to increase gains associated with cognitive training, widely reported in the popular media [7–12]. It is important to note, however, that tDCS in healthy individuals can have a variety of effects on cognition [2,87] (Box 3), including facilitation for some tasks [1,19,20,88–92] and impairment for others [18,19,92–94]. By studying both facilitation and impairment with tDCS we can elucidate the possible mechanisms underlying cognitive and motor training processes. In the following sections we discuss the use of tDCS in cognitive and motor training, and consider its potential to shed light on the neural basis of training effects.

Facilitating training

Several studies have reported that tDCS can facilitate training-related performance improvements in simple motor tasks [92,95,96]. Stagg and colleagues asked participants to respond quickly and accurately to visual cues that were predictable, and led to training-related improvements in reaction times [92,95]. These gains were enhanced when online anodal stimulation was applied to the primary motor cortex [92,95]. Although the mechanisms responsible for such improvements are yet to be fully described, the enhancement seems to be closely linked with GABA concentration in the primary motor cortex [95]. Such approaches have also been translated into treatments for stroke patients [97]. Combining motor training with anodal tDCS over the stroke-affected motor cortex (or cathodal stimulation over the intact motor cortex) leads to significantly greater improvement in motor function of the affected limb than motor training alone [4,98].

Box 3. Predicting the behavioural outcomes of tDCS

Typically, anodal tDCS leads to a facilitation of behavioural performance, whereas cathodal stimulation leads to impaired performance. Such polarity-dependent modulations have been found for motor processing [24–26,92], visual processing [27,28], attention [125,126], working memory [76,127], and language [20]. By contrast, several studies have reported paradoxical stimulation effects, such as enhancement from cathodal stimulation [90,128], and polarity non-specific effects in which both anodal and cathodal stimulation disrupt performance [18,90,93]. Rather than being problematic, we view such paradoxical findings as an opportunity to examine more closely the possible mechanisms underlying the influence of tDCS.

Different effects of tDCS on behaviour have been linked to neural signal-to-noise properties. For example, increased excitability following anodal tDCS might increase the signal of the process(es) of interest, or increase noise in the system, thus effectively burying the signal. Decreased excitability following cathodal tDCS could decrease the signal associated with the process(es) of interest, or it could reduce noise in the system and thereby increase the likelihood of detecting a relatively weak signal. By considering the effects of stimulation in terms of noise, one can account for many of the apparently paradoxical findings with anodal and cathodal tDCS.

An alternative, but related, perspective involves consideration of the codes populations of neurons provide to convey information. For example, if a cognitive process is associated with a specific pattern of activity in a relatively small number of neurons (sparse coding [129]) in a given area, it is possible that either increasing or decreasing local excitability will disrupt these critical patterns. In this way, either anodal or cathodal stimulation might disrupt task specific processing (Figure 2).
tDCS can also facilitate language training. Online anodal stimulation over the left temporoparietal region can facilitate vocabulary learning, compared with sham and cathodal stimulation [20,99]. Moreover, when the left prefrontal cortex is stimulated with online anodal tDCS, language-training benefits in patients with primary progressive aphasia are increased [100]. In a study targeting Broca’s area in aphasic stroke patients, anodal stimulation delivered while patients attempted verbal descriptions of video clips [101] improved the use of connective words in speech discourse [101]. Similarly, for patients with apraxia, completion of language therapy over 10 days with concurrent anodal stimulation of Broca’s area improved accuracy and speed of speech production [102]. Thus, there is emerging evidence that combining language training with online anodal tDCS over relevant brain regions can increase training benefits for healthy individuals and stroke patients.

Two studies have reported benefits of tDCS for the learning of a novel relational-number notation set [19,89]. Here participants learnt values assigned to novel images. These images were presented in pairs, and participants had to learn their relational values, for example, whether the value represented by one image was greater than that of another [19,89]. When stimulation targeted the parietal cortex bilaterally, learning of the values was enhanced [19]. By contrast, performance on a task thought to measure automatic interference between two conflicting stimuli (e.g., where a smaller value symbol is physically bigger than a larger value symbol), showed only a small interference effect between the images, suggesting that automatic processing of the learned digits had been impaired following bilateral parietal stimulation [19]. In the same study, stimulating the dorsolateral frontal cortex impaired number learning and facilitated automaticity [19].

**Disrupting training**

TDCS can also have a negative impact on training outcomes. In Stagg et al. [92] described above, practice-dependent improvements in performance for a simple motor task were magnified by online anodal stimulation. By contrast, stimulating motor cortex disrupted training-related improvements in reaction times when online cathodal stimulation, or offline stimulation of either polarity, was applied [92]. When this finding is considered alongside the facilitation of motor training with online anodal tDCS [92,95,96], an interesting contrast in facilitation and disruption, dependent upon a combination of stimulation timing and polarity, is apparent. This contrast has been used in the development of a neurobiological theory of motor training [47], according to which training effects depend upon synaptic plasticity which can be modulated by tDCS [47].

Mechanisms responsible for simple decision-making or response selection can also be disrupted by anodal or cathodal offline stimulation over the left posterior prefrontal cortex [18,90] (Figure 2). This disruption cannot be attributed to non-specific effects of tDCS, such as changes in arousal, or to the selection of the reference electrode site [18]. Instead, it is thought to reflect disruption in the fine-tuning of response selection codes in the left prefrontal cortex [18,90]. Other high-level processes, such as working memory, can also be impaired by offline tDCS [93,103]. Two studies have described disruption of working memory training, one following bilateral stimulation of the parietal cortex [103], and the other following anodal or cathodal stimulation of the cerebellum [93].

It is noteworthy that studies reporting disruption of training with tDCS used offline stimulation designs (or online cathodal stimulation [92]), and all but one [103] employed unilateral stimulation montages focusing on a specific target region. Thus, there is consistency between studies concerning the effects of stimulation polarity and timing. This consistency implies common neural mechanisms for training across a range of motor and cognitive tasks. The precise nature of these mechanisms is yet to be fully described and tested, although they may relate to processes of neural tuning of activity with training [18], or modulations in synaptic plasticity [47], with a key role for the neurotransmitter GABA [95]. TDCS can provide a unique perspective on the mechanisms involved in cognitive and motor training, substantially adding to our understanding of training-related neural processes.

**Methodological considerations**

TDCS studies have made a substantial contribution to our understanding of the neural basis of perception, cognition, and motor behaviour. Nevertheless, there is considerable scope for extension of the existing research in these fields (Box 4). However, as with all approaches, there are several methodological issues that can limit the interpretation of findings. We address some potential pitfalls here.

**Baseline measures**

Many TDCS experiments include ‘sham’ stimulation as a baseline against which to compare the effects of active stimulation. Typically, a sham condition will involve substantially reduced current flow, either in terms of duration or intensity, relative to an active stimulation condition. It is widely assumed that participants cannot distinguish sham from active stimulation [104], but concerns have been raised regarding the validity of this assumption [37,105]. Even when participants cannot consciously discriminate sham and active stimulation, there may nevertheless be differences in other factors, such as arousal. It is therefore crucial that appropriate control conditions are incorporated into experimental designs. Such conditions could involve contrasting anodal and cathodal stimulation effects, conducting a control experiment in which an alternative electrode montage is used that does not target the region of interest, or using a different stimulation frequency or phasic alignment (in the case of oscillatory tDCS).

**Specificity of stimulation**

Models of tDCS current flow [14,106–111] and findings from studies in which human fMRI has been used to measure brain activity [15,33,112] suggest that tDCS can alter processing across large areas of cortex. In this sense, the effects of tDCS are likely to be relatively broad. Thus, while the neural changes induced by tDCS are concentrated around regions of cortex closest to the
electrodes [110], broader networks of functionally connected regions may also be recruited [15,16,33,34], suggesting a fruitful direction for future research on the human connectome [113]. At present, researchers should be circumspect when linking a specific process to a small area of cortex on the basis of tDCS results.

In terms of spatial specificity, it is important that effects of tDCS in the vicinity of any reference electrode are taken into account. Indeed, it is possible that any reported effects of tDCS on behaviour are due to stimulation at the reference electrode, or an interaction between the target and reference sites. This can only be ruled out by conducting
control experiments with alternative reference locations [18], or by using a large reference electrode. The use of a large reference electrode reduces the current density applied to the reference location. If the current density is sufficiently low it will reduce any effect of stimulation at this location. By conducting follow-up experiments to rule out effects of stimulation at the reference site, there is the added advantage of offering an opportunity to replicate the original findings [114].

Specifying the neurological basis of stimulation effects

It is common for training studies to use a combination of online and offline stimulation [19,89,92,99]. In such cases, both the stimulation and the task commence together, but the task continues after stimulation has ended. Given the differences between the effects of online and offline stimulation on behaviour (see 'Cognitive and motor training'), it is difficult to speculate about the mechanisms behind facilitation with this design. In addition, designs in which a bilateral stimulation montage is used make it difficult to apportion effects specifically to the anode or the cathode. Any such problem in separating anodal and cathodal effects will inevitably restrict conclusions about the underlying neurobiological mechanisms.

Concluding remarks and future directions

tDCS has a variety of effects on the cortex, including modulations in membrane polarisation and excitability [22] that are stimulation-polarity dependent [23–26,92]. It can also modulate GABA [47,48,51,52], glutamate [48,50,52], acetylcholine [39,68], serotonin [57] and dopamine [55,56] systems. The precise effect of stimulation is determined to some extent by the prior state of the cortex [43,45]. tDCS has already provided key insights into learning and memory processes, and how these rely upon different areas of the cerebral cortex [73,79,80]. Research using this technique has also shown that oscillation frequency and phase are important factors in perception [84,85]. When combined with fMRI, tDCS can identify underlying functional brain networks [16,64,65,69], and when paired with TMS it can modulate these networks [67,68]. Studies employing tDCS have provided causal evidence for the neural processes underlying performance benefits from training. Further, stimulation can both enhance [19,20,89,92,99] and impair [18,90,92,93,103] the effects of training, depending on stimulation timing and polarity.

The ability of tDCS to modulate neurobiological processes has given a unique perspective on the mechanisms underlying perception, cognition, and action. In the future, carefully designed tDCS studies should provide further advances in our understanding of the neural processes involved in performance gains from cognitive training, the role of oscillations in neural communication, and the elucidation of functional neural networks. Moreover, there is potential for the development of treatments for a variety of neurological and psychiatric conditions.

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