

Applications of transcranial direct current stimulation for understanding brain function

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Box 2: modelling current flow – 259 words

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Abstract

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.

Keywords: tDCS, neural oscillations, training, memory, prefrontal cortex, neural processes

Introduction to the use of tDCS in neuroscience

Transcranial direct current stimulation (tDCS) 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] (see 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 article, 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.

Neurobiological effects of tDCS

Excitability changes induced by tDCS

Animal studies have shown that anodal stimulation applied directly to the cortex causes a reduction in the resting membrane potential, 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 (1mA) stimulation causes conventional polarity-specific modulation of neural excitability, higher intensity (2mA) 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 (see 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 a known influencing factor in 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 5Hz stimulation [41]) or decreased excitability (e.g., with 1Hz stimulation [42]). If the motor cortex is pre-conditioned 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 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].

As 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 a neuron's membrane potential.

Further evidence that tDCS modulates synaptic activity via neurotransmitters has come from human studies using magnetic resonance spectroscopy (MRS) [48, 49], and from drug studies targeting specific neurotransmitter receptors [50, 51]. These studies have reported that anodal stimulation inhibits GABA [47, 48, 51, 52] (a known inhibitory neurotransmitter [53]), whereas cathodal stimulation inhibits glutamate [48, 50, 52] (a known excitatory neurotransmitter [54]) (Figure 1). Such modulations of synaptic processes suggest that tDCS influences synaptic plasticity [47], and that GABA and glutamate play a role in the effects of tDCS on brain function.

Several drug interventions have linked the neuromodulators serotonin and dopamine to tDCS aftereffects [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 [48, 51, 52, 59], 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 (Box 4).

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 [60]. 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. These include the default mode network [61], which includes the inferior parietal, medial temporal, and medial prefrontal cortices [62], and which shows slow-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 [63] and the cingulo-opercular network [64].

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 prefrontal cortex, and primary and secondary motor cortices [65]. tDCS over prefrontal cortex induces alterations in both the default mode and fronto-parietal networks [66]. 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 [67].

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 [68]. These findings suggest that the SMA region has an inhibitory input to the motor cortex, and an excitatory input to the somatosensory cortex [68]. In another study, Feurra et al. [69] 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 [69], relative to sham stimulation, suggesting a parieto-motor circuit is involved in motor imagery [69].

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 [70]. 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 [71, 72].

Modulating neural communication

Endogenous oscillations in neural activity provide an important means of communication between distant sites across the brain [73]. For example, slow-wave oscillations between the neocortex and hippocampus during sleep are thought to be important for long-term memory formation [74, 75]. There is evidence that conventional anodal or cathodal tDCS can cause changes in oscillatory cortical activity in the theta [76, 77], alpha [77], beta [76, 78], and gamma [78] range. 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 [79] and humans [74, 80, 81] is enhanced. Likewise, the same oscillatory tDCS protocol can improve learning of new information during wakefulness [82]. 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 [76, 78].

In-phase oscillations across sensory and parietal cortices have been identified as important factors in perception [83, 84]. Neuling et al. (2012) confirmed the importance of in-phase activity by applying 10 Hz oscillatory tDCS to the auditory cortex [85]. When the oscillations were in-phase with an auditory

stimulus, detection was improved relative to when oscillations were out of phase with the stimulus [85]. Gamma frequency oscillations in the occipito-parietal cortex have also been implicated in visual bistable motion perception [86], with tDCS induced gamma, but not theta, oscillations reducing perceptual switches in motion direction [86]. This reduction presumably reflects 'blocking' of changes in frequency that typically trigger shifts in perceived motion direction for bistable stimuli [86].

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 [85, 86], learning [82], and memory [74, 80, 81]. 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, 87]. 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, 88] (Box 3), including facilitation for some tasks [1, 19, 20, 89-93] and impairment for others [18, 19, 93-95]. 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 [93, 96, 97]. 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 [93, 96]. These gains were enhanced when online anodal stimulation was applied to the primary motor cortex [93, 96]. 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 [96]. Such approaches have also been translated into treatments for stroke patients [98]. 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, 99].

tDCS can also facilitate language training. Online anodal stimulation over the left temporo-parietal region can facilitate vocabulary learning, compared with sham and cathodal stimulation [20, 100]. Moreover, when the left prefrontal cortex is stimulated with online anodal tDCS, language training benefits in patients with primary progressive aphasia are increased [101]. In a study

targeting Broca's area in aphasic stroke patients, anodal stimulation delivered while patients attempted verbal descriptions of video clips [102] improved the use of connective words in speech discourse [102]. Similarly, for patients with apraxia, completion of language therapy over ten days with concurrent anodal stimulation of Broca's area improved accuracy and speed of speech production [103]. 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, 90]. Here participants learnt values assigned to novel images. These images were presented in pairs, and participants had to learn their relational values, e.g., whether the value represented by one image was greater than that of another [19, 90]. 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. (2011), 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 [93]. When this finding is considered alongside the facilitation of motor training with online anodal tDCS [93, 96, 97], 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 [59], according to which training effects depend upon synaptic plasticity which can be modulated by tDCS [59].

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, 91] (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, 91]. Other high-level processes, such as working memory, can also be impaired by offline tDCS [104, 105]. Two studies have described disruption of working memory training, one following bilateral stimulation of the parietal cortex [105], and the other following anodal or cathodal stimulation of the cerebellum [104].

It is noteworthy that studies reporting disruption of training with tDCS used offline stimulation designs (or online cathodal stimulation [93]), and all but one [105] 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 [96]. 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, like any approach, there are a number of 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 [106], but concerns have been raised regarding the validity of this assumption [37, 107]. 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, 108-113] and findings from studies in which human fMRI has been used to measure brain activity [15, 33, 114] 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 [112], 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 [115]. 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 [116].

Specifying the neurological basis of stimulation effects

It is common for training studies to use a combination of online and offline stimulation [19, 90, 93, 100]. 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.

Summary

tDCS has a variety of effects on the cortex, including modulations in membrane polarisation and excitability [22] that are stimulation-polarity dependent [23-26, 93]. It can also modulate GABA [48, 51, 52, 59], glutamate [48, 50, 52], acetylcholine [39, 58], 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 [74, 80, 81]. Research using this technique has also shown that oscillation frequency and phase are important factors in perception [85, 86]. When combined with fMRI, tDCS can identify underlying functional brain networks [16, 65, 66, 70], and when paired with TMS it can modulate these networks [68, 69]. Studies employing tDCS have provided causal evidence for the neural processes underlying performance benefits from training. Further, stimulation can both enhance [19, 20, 90, 93, 100] and impair [18, 91, 93, 104, 105] 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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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 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 minutes). 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 cognitive processes, including working memory, language, mathematical learning, spatial attention, and response selection (Table 1). Recently, tDCS has been shown to modulate high-level processes such as social norm compliance [117]. Clinical applications for a number of conditions exist, with evidence 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 blood-oxygen-level-dependent signal is the dependent variable), tDCS can provide causal evidence that a brain region is involved in a behaviour(s) of interest. tDCS offers a perspective that is unique with respect to other brain stimulation methods, such as transcranial direct current stimulation (TMS). For example, tDCS influences a larger region(s) 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 (scalp tingling); it produces fewer physiological artefacts than TMS (e.g. muscle twitches and auditory noise); 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 so each electrode does not remain polarity specific [118]. 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 [119, 120] and as a clinical treatment [121]. The idea of adding neural noise to a system, and finding resulting improvement, may seem counterintuitive. However, the enhancement of a signal through the addition of noise can be explained via stochastic resonance

[122], whereby a weak signal is boosted by an increase in background noise
[122].

Box 2: Modelling current flow

Several mathematical models have been developed to describe the path of current flow in cortical tissue induced by tDCS [14, 108, 109, 111-113]. 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) [112]. 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, 112].

As a rule, the strongest current is induced at cortical locations that are nearest the electrodes [112]. Current density generally diminishes with increasing distance from the electrodes [112], 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, e.g., 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 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, 93], visual processing [27, 28], attention [125, 126], working memory [77, 127], and language [20]. By contrast, a number of studies have reported paradoxical stimulation effects, such as enhancement from cathodal stimulation [91, 128], and polarity non-specific effects in which both anodal and cathodal stimulation disrupt performance [18, 91, 104]. Rather than being problematic, we view such paradoxical findings as an opportunity to more closely examine 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 alternate, 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 (see Figure 2).

Box 4: Future research directions

Neurobiological effects of tDCS

- *What are the consequences of tDCS on neural processes?* While tDCS can modulate membrane potentials [22] and synaptic processes [48, 52, 58], the mechanisms underlying polarity-specific modulations remain unclear. Future research should employ invasive measures, e.g. direct recordings in non-human primates, to better understand how tDCS alters neural functioning. This will reveal how tDCS modulates synaptic plasticity and influences behaviour.
- *How are the effects of stimulation altered by the state of the cortex?* The effects of tDCS and TMS can interact when applied consecutively [43, 45]. Such interactions suggest a relationship between neural changes induced via tDCS and the state of the cortex at the time stimulation is applied. Future research should systematically manipulate the prior state of the cortex (e.g., through TMS, behavioural tasks, or training) to understand the factors that can alter tDCS efficiency, and how tDCS protocols can be tailored to maximize the size and consistency of modulations.

The role of oscillations in cognition

- *What roles do neural oscillations play in brain function?*

Studies using oscillatory tDCS have shown that neural oscillatory frequency and phase are important for perception [85, 86] and cognition [74, 80]. Understanding the roles of these two components of oscillations will require systematic manipulation of oscillatory frequency and phase, and the comparison of these two factors for different cognitive processes (e.g. learning and perception).

Neural bases of cognitive training

- *What are the roles of stimulation timing and polarity?* Stimulation timing (online vs. offline) and polarity (anode and cathode) have distinct effects on the cortex. Research into cognitive training can utilize these distinct effects of stimulation timing and polarity with carefully controlled experimental designs [18, 91, 93]. If this approach is applied to a broad range of training paradigms, researchers will be able to pinpoint the neural mechanisms that lead to training related changes in performance.
- *What are the neural bases of training?* Combining tDCS with neuroimaging techniques (e.g., fMRI and MRS) may elucidate the neural bases of training effects, how these training induced changes are modified by stimulation, and the network(s)/brain regions involved in the training process.
- *How long can modulations due to tDCS and training last?* There is relatively little information on how long the effects of tDCS on cognitive and motor training may last. It will be crucial to establish the potential efficiency of tDCS for inducing long-term modulations in behaviour.

Clinical applications of tDCS

- *How may tDCS improve clinical symptoms?* tDCS has shown promise as a simple, cheap, non-invasive treatment for a variety of clinical conditions [3-6]. Conditions such as depression and stroke are characterized by local and widespread changes in brain structure [130], connectivity [130, 131] and function [130, 131]. Future research should address how such features of clinical conditions are modulated by tDCS. This approach will allow for the tailoring of tDCS interventions to maximise treatment benefits.

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.

Cathode: an electrode with a negative charge.

Cathodal tDCS: stimulation applied via the cathode, typically associated with decreased cortical excitability and decreased levels of the neurotransmitter glutamate.

EEG: electroencephalography. Measurement of electrical activity on the scalp, typically via multiple electrodes. Neural activity is reflected by small changes in electrical potential.

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.

Magnetic resonance spectroscopy (MRS): type of magnetic resonance imaging that allows for the non-invasive measurement of metabolites (including neurotransmitters). MRS provides the concentrations of detectable metabolites in the measured area of the brain.

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.

Region of interest (ROI): an area of the cortex targeted with tDCS.

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.

Resting state fMRI (rsfMRI): measurement of the blood oxygen level dependent (BOLD) signal whilst a participant is at rest. rsfMRI allows analysis of brain activity and networks in the absence of any specific task.

Plasticity: changes in structural or functional pathways in the brain in response to experience.

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 minutes), 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.

Table 1: Summary of key papers reporting behavioural modulations through tDCS

Key studies that have demonstrated tDCS modulations of behaviour. Here 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 the key findings are given for each study.

Figure 1: The neurobiological effects of tDCS

A: Illustration of a typical tDCS montage for targeting the prefrontal cortex.

The anode (red; target electrode) is placed over the prefrontal cortex (equivalent to F3 in the EEG 10-20 system) and the cathode (blue; reference electrode) over orbitofrontal cortex. The current flows from the anode to the cathode, and modulates the cortex underneath and between the electrodes.

This image is for illustrative purposes only and not based on a mathematical model.

B: Firing rates recorded from neural populations in cats. Anodal stimulation led to an elevated firing rate, and cathodal stimulation led to a decreased firing rate. Reproduced from Purpura et al (1969) with permission.

C: Simplified diagram showing a presynaptic and a postsynaptic GABAergic neuron. Anodal stimulation inhibits GABA. **D:** A simplified diagram showing a presynaptic and a postsynaptic glutamatergic neuron. Cathodal stimulation inhibits glutamate.

Figure 2: A demonstration of polarity non-specific disruption of response selection training (Filmer et al., 2013)

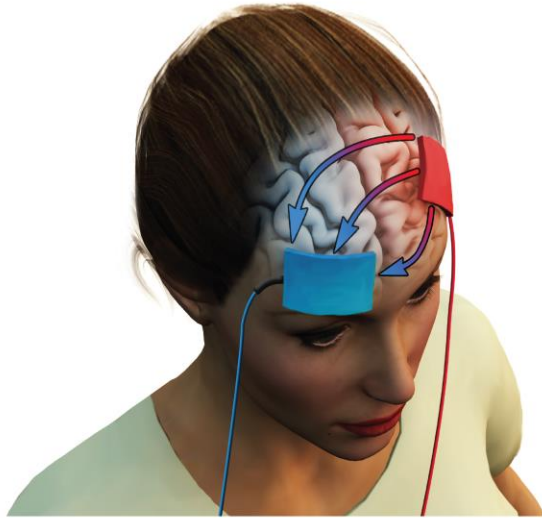
A: Session outline. Participants practiced a response selection task, and then completed a pre-tDCS baseline block of the task. Stimulation was then administered, followed by an immediate-post tDCS block of the task. After a 10-minute wait (no task), participants completed the final block of the paradigm (20-minutes post-tDCS). **B:** Example trial outline. Participants were given an initial fixation period, followed by a colour, symbol, or a sound. Participants were instructed to respond to the image or sound as quickly and accurately as possible. The task was a 6-alternative, forced-choice, with six different possible colours, symbols, or sounds and six corresponding keys on the keyboard. Participants completed three sessions of the experiment, with one stimulus type used in each session (colours, symbols, and sounds). **C:** Schematic depiction of stimulation types. Anodal stimulation was delivered with a constant (positive) current lasting eight minutes. Cathodal stimulation was delivered with a constant (negative) current lasting eight minutes. Sham stimulation consisted of an initial, constant current for 15 seconds only. In all conditions, the current was initially ramped on over 30 seconds and at the end ramped off over 30 seconds. One type of stimulation was administered in a single session, with a minimum of 48 hours between sessions. **D:** Electrode montages used across three experiments. Experiment 1 targeted the left prefrontal cortex (1 cm posterior to F3), with the reference location over right orbitofrontal cortex. Experiment 2 targeted the right prefrontal cortex, with the reference over left orbitofrontal cortex. Experiment 3 targeted the left prefrontal cortex, with the reference over right prefrontal cortex. **E:** The

difference in reaction times from before to immediately after, and 20 minutes after, tDCS. A positive number reflects improved performance (shorter reaction times). Data for the anodal condition are shown in red, the cathodal condition in blue, and the sham condition in black. All three stimulation experiments yielded improved reaction times for the sham condition, as did the two active stimulation conditions for Experiment 2 (right prefrontal cortex stimulation). For the two experiments targeting the left prefrontal cortex, both anodal and cathodal stimulation disrupted the training effect.

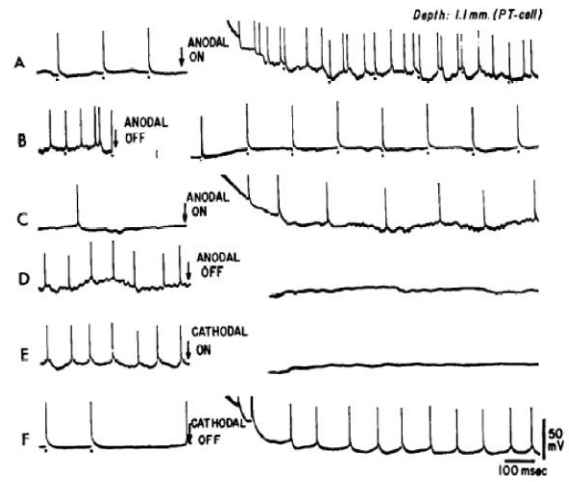
Table 1

	Reference	Location and size of target electrode(s)	Location of reference electrode	tDCS parameters	Stimulation types	tDCS protocol	Sample size and design	Findings
Response selection	Filmer et al., 2013 [18]	Left pLPFC, 25cm ²	Right orbitofrontal	0.7mA for 9 minutes	Anodal, cathodal, and sham	Offline	18, within participants	Anodal and cathodal tDCS, compared with sham tDCS, impaired training related improvements in response selection.
	Filmer et al., 2013 [91]	Left pLPFC, 25cm ²	Right orbitofrontal	0.7mA for 9 minutes	Anodal, cathodal, and sham	Offline	18, within participants	Single task: anodal and cathodal tDCS disrupted response selection training. Dual task: cathodal stimulation increased response speed.
Mathematical learning	Iuculano & Kadosh, 2013 [19]	Bilateral PPC or DLPFC (anode left, cathode right), 3 cm ²	N/A	1mA for 20 minutes	Active and sham	Online and offline	19, between participants	PPC tDCS, compared to sham tDCS, increased learning rate of novel symbolic 'numbers', decreased the automatic interference between novel numbers. DLPFC tDCS led to the opposite pattern.
Language learning	Meinzer et al., 2014 [20]	Left TJP, 35cm ²	Right orbitofrontal	1mA for 20 minutes	Anodal and sham	Online	40, between participants	Five consecutive days of anodal tDCS, compared with sham, improved learning of novel words. Some benefit remained one week later.
	Floel et al, 2008 [100]	Wernicke's area, 35cm ²	Right orbitofrontal	1mA for 20 minutes	Anodal, cathodal, and sham	Online and offline	19, within participants	Anodal tDCS, compared with cathodal and sham tDCS, improved learning of novel words.
Perception/ Detection	Clark et al, 2012 [89]	Right inferior frontal cortex	Right sphenoid bone	2mA or 0.1mA for 30 minutes	Anodal, tDCS high (2mA) and low (0.1mA) intensity	Online and offline	27, between participants	High, but not low, intensity tDCS improved accuracy at detecting concealed objects in a virtual reality task.
Working memory	Martin et al., 2013 [132]	Left DLPFC, 35cm ²	Right deltoid muscle, 100cm ²	2mA for 30 minutes	Active tDCS, sham tDCS plus training, active tDCS plus training	Online	54, between participants	Stimulation over 10 consecutive weekdays improved working memory performance (dual-task n-back). No improvement without concurrent tDCS.
	Sandrini et al, 2012 [105]	Bilateral PPC, 35cm ²	N/A	1.5mA for 13 minutes	Anode left or right PPC, cathode opposite hemisphere sham	Offline	27, between participants	Low working memory load: training abolished with left anodal/right cathodal tDCS. High working memory load: practice related improvements abolished with right anodal/left cathodal tDCS.
Motor skill acquisition	Reis et al., 2009 [92]	Left M1, 25cm ²	Right orbitofrontal	1mA for 20 minutes	Anodal and sham	Online and offline	24, between participants	Anodal (compared to cathodal and sham) tDCS increased the speed of motor skill acquisition. Benefits remained at a 3-month follow up.
Error awareness	Harty et al., 2014 [133]	Left or right DLPFC	Cz (vertex)	1mA for duration of task	Anodal, cathodal, and sham	Online	24, between and within participants	Anodal tDCS to the right DLPFC improved error detection in healthy older adults. Anodal tDCS to the right DLPFC, or cathodal or sham to the left DLPFC, had no effect on error awareness.

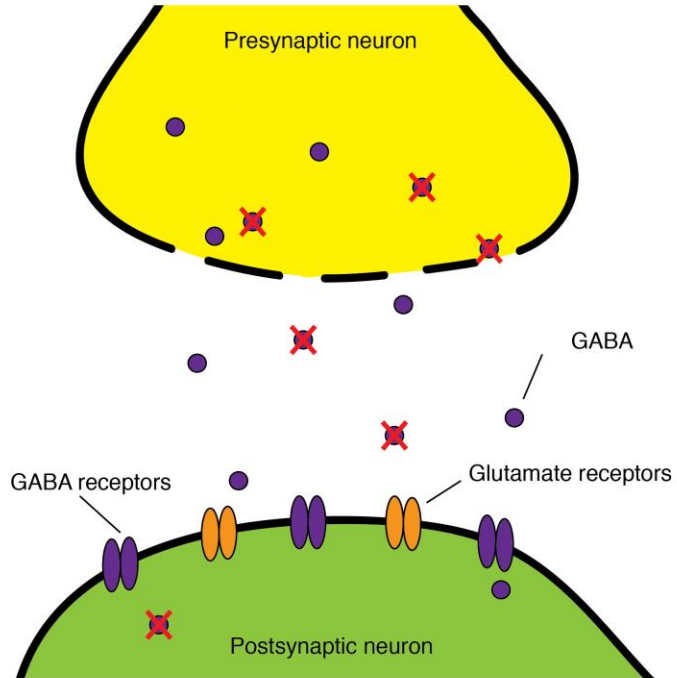
A



B



C



D

