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Review

The use of tDCS and CVS as methods of non-invasive brain stimulation

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ARTICLE INFO

Article history:

Accepted 19 August 2007

Available online 28 August 2007

Keywords:

Transcranial direct current stimulation
Caloric vestibular stimulation
Brain stimulation
Transcranial magnetic stimulation
Stroke
Mood disorder

ABSTRACT

Transcranial direct current stimulation (tDCS) and caloric vestibular stimulation (CVS) are safe methods for selectively modulating cortical excitability and activation, respectively, which have recently received increased interest regarding possible clinical applications. tDCS involves the application of low currents to the scalp via cathodal and anodal electrodes and has been shown to affect a range of motor, somatosensory, visual, affective and cognitive functions. Therapeutic effects have been demonstrated in clinical trials of tDCS for a variety of conditions including tinnitus, post-stroke motor deficits, fibromyalgia, depression, epilepsy and Parkinson's disease. Its effects can be modulated by combination with pharmacological treatment and it may influence the efficacy of other neurostimulatory techniques such as transcranial magnetic stimulation. CVS involves irrigating the auditory canal with cold water which induces a temperature gradient across the semicircular canals of the vestibular apparatus. This has been shown in functional brain-imaging studies to result in activation in several contralateral cortical and subcortical brain regions. CVS has also been shown to have effects on a wide range of visual and cognitive phenomena, as well as on post-stroke conditions, mania and chronic pain states. Both these techniques have been shown to modulate a range of brain functions, and display potential as clinical treatments. Importantly, they are both inexpensive relative to other brain stimulation techniques such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS).

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Contents

1. Introduction	347
2. Transcranial direct current stimulation	347
2.1. Background	347
2.2. Mechanism of action.	347
2.3. Safety	348
2.4. Effects on motor cortex	348

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Abbreviations: BR, binocular rivalry; CVS, caloric vestibular stimulation; ES, electronic stimulation; NMV, neck muscle vibration; RVS, rotational vestibular stimulation; TPA, temporoparietal areas

2.5.	Effects on visual cortex	348
2.6.	Effects on somatosensory cortex	349
2.7.	Effects on cognition and mood	349
2.8.	Therapeutic effects	349
2.9.	tDCS, TMS priming and pharmacological modulation	350
2.10.	Summary	351
3.	Caloric vestibular stimulation	351
3.1.	Background	351
3.2.	Experimental technique and safety	351
3.3.	Brain imaging studies	351
3.4.	Effects on vision and cognition	353
3.5.	Effects on neglect and other post-lesional conditions	354
3.6.	Effects on mood disorders	354
3.7.	Effects on pain disorders	355
3.8.	Summary	355
4.	Overall summary	355
	Acknowledgments	355
	References	355

1. Introduction

Multiple new brain stimulation techniques are currently under investigation, including transcranial magnetic stimulation (TMS), deep brain stimulation, magnetic seizure therapy and vagus nerve stimulation (Eitan and Lerer, 2006; Fitzgerald, 2006). Apart from TMS, these therapies are invasive or convulsive and all of them suffer from the drawback of currently being expensive to administer. TMS has been used to study the excitability of the cortex, cortical regional connectivity, the plasticity of brain responses and cognitive functioning in illness and disease states (Fitzgerald et al., 2002a,b). It has also been shown to be potentially effective as a treatment for depression (Fitzgerald et al., 2006a; Garcia-Toro et al., 2006; Isenberg et al., 2005) as well as for the positive and negative symptoms of schizophrenia (Brunelin et al., 2006; Lee et al., 2005; Poulet et al., 2005). Advances in brain-imaging techniques have allowed progress towards the identification of brain regions to be targeted in cognitive and clinical TMS studies. An advantage of TMS is that it allows stimulation of such regions that subservise particular cognitive functions and that are implicated in particular clinical disorders. Expanding the repertoire of available neurostimulation techniques can take therefore advantage of this increased functional-anatomic understanding of the human brain.

Two non-invasive and non-convulsive techniques for altering brain function are transcranial direct current stimulation (tDCS) and caloric vestibular stimulation (CVS). tDCS offers the possibility of regulating cortical excitability and CVS allows selective activation of structures within either the left or right cerebral hemisphere. Both techniques are non-invasive, do not seem to produce serious side effects and are inexpensive to administer.

2. Transcranial direct current stimulation

2.1. Background

Transcranial direct current stimulation is a non-invasive method for modulating cortical excitability that has undergone resur-

gence in recent years. Systematic investigations of direct current stimulation date from the 1960s but despite some encouraging reports, the method never gained in clinical popularity (for a review, see Priori, 2003).

Recent increased understanding of central nervous system (CNS) function and pathology, along with new techniques for investigating brain activation such as TMS, have facilitated a more comprehensive understanding of the effects of tDCS and supported the development of potential clinical applications. Protocols that are currently used have produced no significant adverse effects and as further investigation of more powerful protocols and novel applications proceeds, tDCS shows promise as an effective and versatile neurostimulation tool.

2.2. Mechanism of action

Contemporary tDCS protocols generally involve the application of two surface electrodes, one serving as the anode and the other as the cathode. A 1 mA or 2 mA direct current is applied for up to 20 min between two 35 cm² (5 cm × 7 cm) electrodes placed on the scalp. The current flows from the anode to the cathode, some being diverted through the scalp and some moving through the brain, and leads to increases or decreases in cortical excitability dependent on the direction and intensity of the current (Miranda et al., 2006). The effects of a single-stimulation session persist for up to 1 h post-stimulation without any additional pharmacological or other intervention (Nitsche and Paulus, 2001). Anodal tDCS typically has an excitatory effect on the local cerebral cortex by depolarising neurons, while the converse applies under the cathode through a process of hyperpolarisation (Nitsche et al., 2003). In relation to electrode size, increasing the size of the reference electrode and reducing the size of the stimulation electrode allows for more focal treatment effects (Nitsche et al., 2007a).

Pharmacological studies offer some clues to tDCS's mechanism of action. These studies have analysed effects produced within short trains and the persisting effects found after longer stimulation trains. Sodium and calcium channel blockers eliminate both the immediate and longer term effects

of anodal stimulation while blocking NMDA (glutamate) receptors prevents the long-term effects of tDCS, regardless of direction (Nitsche et al., 2003).

Ardolino et al. (2005) studied the effects of cathodal tDCS on spontaneous neural activity and on motor responses evoked by stimulation of the central and peripheral nervous system, and concluded that the after-effects of tDCS have a non-synaptic mechanism of action based on changes in neural membrane function. They suggested a number of mechanisms for the effects including local changes in ionic concentrations, alterations in transmembrane proteins and electrolysis-related changes in hydrogen ion concentration induced by exposure to a constant electric field. Nitsche et al. (2005) investigated the short- and long-term effects of anodal and cathodal tDCS on the motor cortex by measuring changes produced by such stimulation on TMS parameters, including intracortical inhibition and facilitation as well as indirect-wave (I-wave) interactions. Motor cortex I-waves are corticospinal waves following the first corticospinal volley that are probably under the control of intracortical neuronal circuits (Nitsche et al., 2005), which are increased following more than ten stimuli of suprathreshold rTMS (Di Lazzaro et al., 2002).

During stimulation, cathodal tDCS reduced intracortical facilitation. At post-stimulation, anodal tDCS increased facilitation and reduced inhibition, with the inverse applying for cathodal tDCS. The effects on cortical inhibition suggested that tDCS modulates the excitability of both inhibitory interneurons as well as excitatory neurones. Furthermore, anodal stimulation had a significant positive effect on I-wave facilitation. I-waves are modulated by GABAergic drugs and ketamine, an NMDA-receptor antagonist, but not by ion channel blockers (Ghaly et al., 2001; Ziemann et al., 1998), thus implicating effects on inhibitory synaptic pathways in the mechanism of action of anodal stimulation.

The effects produced by tDCS have a number of features characteristic of the induction of synaptic neuroplastic processes including the duration of its effects being dependent on stimulation intensity, its intracortical origin and its apparent dependence of NMDA-receptor activity (Paulus, 2004). In summary, the mechanism of action of tDCS is not completely clear but appears to involve a combination of hyper- and de-polarising effects on neuronal axons as well as alterations in synaptic function.

2.3. Safety

The use of tDCS in protocols to date has not resulted in significant adverse effects, apart from mild headache or itching underneath the electrodes (Fregni et al., 2006a; Poreisz et al., 2007). tDCS does not cause heating effects under the electrodes and does not elevate serum neurone-specific enolase level (Nitsche and Paulus, 2001), a sensitive marker of neuronal damage, nor does it induce brain oedema or alterations of the blood-brain barrier and cerebral tissue that are detectable by magnetic resonance imaging (MRI) (Nitsche et al., 2004a). Furthermore, no adverse cognitive effects were noted following a treatment protocol effective in alleviating depression (Fregni et al., 2006b). However, there may be safety issues with tDCS that only emerge with larger studies.

2.4. Effects on motor cortex

Among the wide variety of brain functions that have been shown to be modulated by tDCS, a number of studies have explored its effects in motor cortex. Lang et al. (2004b) tested ipsi- and contralateral motor-evoked potentials (MEPs) following anodal or cathodal stimulation to left primary motor cortex (M1) and found an increase in response from the stimulated hemisphere following anodal tDCS and a decrease following cathodal tDCS. It was further shown that transcallosal inhibition from left M1 remained unchanged whereas the duration of transcallosal inhibition evoked from the right M1 was shortened after cathodal tDCS and prolonged after anodal tDCS. The authors suggested that the effects of tDCS are limited to the stimulated hemisphere, including inhibitory interneurons mediating transcallosal inhibition from the contralateral hemisphere. Quartarone et al. (2004) reported that during motor imagery, MEPs measured with TMS were reduced following cathodal tDCS whereas there was no effect following anodal stimulation. The after-effects of tDCS on motor cortex excitability have also been reported to be absent in patients with sporadic amyotrophic lateral sclerosis (Quartarone et al., 2007).

There are also other functional implications of motor cortical stimulation. For example, regardless of polarity, tDCS has been shown to reduce the influence of training on the direction of a TMS-induced hand twitch when it is applied during the training (Rosenkranz et al., 2000). In addition, it has been shown that non-dominant hand motor function can be improved by anodal stimulation to the non-dominant M1 (Boggio et al., 2006a). When measured by blood oxygen level-dependent MRI, cathodal stimulation over the sensorimotor cortex has been found to significantly decrease activation, while anodal stimulation resulted in a non-significant increase in activation (Baudewig et al., 2001). tDCS can have effects on the cortex that are remote from the sites of electrode placement. For example, positron emission tomography (PET) has been used to measure regional cerebral blood flow (rCBF) at rest and during finger movements following 10 min of sham, cathodal or anodal tDCS over the primary motor hand areas and right frontopolar cortex. It was found that there were relative increases in activation of left M1, right frontal pole, right primary sensorimotor cortex and posterior brain regions, independent of the polarity in the non-sham conditions (Lang et al., 2005). Furthermore, anodal stimulation increased rCBF relative to the cathodal condition in many cortical and subcortical areas. This suggests that tDCS has the capacity to induce changes across neural networks, even without producing the direct firing of projecting neurones.

2.5. Effects on visual cortex

The effects of tDCS have been explored in a range of visual paradigms. First, consistent with the effects on excitability in motor cortex, moving and stationary phosphene thresholds induced by TMS have been found to be increased by cathodal tDCS and reduced by anodal tDCS applied to the occipital cortex (Antal et al., 2003a,b). Other visual paradigms have also been used in studying the effects of tDCS. Both static and dynamic contrast sensitivities are reduced by cathodal tDCS

(Antal et al., 2001) and the N70 peak of visual-evoked potentials (VEPs) were increased by anodal and decreased by cathodal stimulation (Antal et al., 2004a). Accornero et al. (2007) found a different effect on the P100 peak of VEPs, with anodal stimulation decreasing the amplitude and cathodal stimulation increasing the amplitude. Another study measuring the N70 peak of VEPs found that cathodal stimulation significantly decreased while anodal stimulation slightly (non-significantly) increased the normalized beta and gamma frequency powers (Antal et al., 2004b), suggesting a possible role for tDCS in influencing higher-order cognitive processes linked to gamma frequencies (e.g., Herrmann et al., 2004). Finally, in relation to extrastriate areas, cathodal stimulation over V5 has been shown to improve visual tracking (Antal et al., 2004c).

2.6. Effects on somatosensory cortex

Like the reported effects of tDCS on motor and visual cortex, a small number of studies on somatosensory cortex have found bimodal effects of anodal and cathodal tDCS with potential functional implications. Anodal tDCS to the sensorimotor cortex has also been shown to increase somatosensory potentials resulting from stimulation of the right median nerve (Matsunaga et al., 2004) whereas cathodal stimulation has been found to reduce low- but not high-frequency components of sensory-evoked potentials following median nerve stimulation (Dieckhöfer et al., 2006). Similarly, cathodal but not anodal or sham stimulation to the somatosensory cortex decreased tactile discrimination of vibratory stimulation to the left ring finger (Rogalewski et al., 2004).

2.7. Effects on cognition and mood

A limited number of studies that have explored the effects of tDCS on cognitive functioning suggest the potential of the technique to both enhance and disrupt performance. Most of these studies have targeted prefrontal regions which are of interest due to the well-known involvement of impaired function in these regions in psychiatric disorders such as depression and schizophrenia (Drevets, 2000; Fitzgerald et al., 2006b; Reid et al., 2002; Shamay-Tsoory et al., 2006). For example, implicit probabilistic classification learning is facilitated by anodal tDCS to the left prefrontal cortex (Kincses et al., 2004), as is working memory during a sequential-letter working memory task (Fregni et al., 2005) and a three-back task in patients with Parkinson's disease (Boggio et al., 2006b).

Other cognitive effects in prefrontal cortex have recently been shown whereby anodal tDCS over either the left or right dorsolateral prefrontal cortex (DLPFC) with the cathode over the contralateral DLPFC decreased risk taking behaviour during ambiguous decision-making (Fecteau et al., 2007). However, intermittent bifrontal tDCS has been found to impair reaction time in a working memory task, regardless of polarity (Marshall et al., 2005). Other studies have also explored the cognitive effects of tDCS applied during sleep. For example, when applied bilaterally over the frontal areas during slow-wave sleep, anodal tDCS was found to significantly increase word-pair retention (Marshall et al., 2004). In the same experiment, bifrontal anodal tDCS was reported to improve

mood, regardless of whether it was applied during waking or sleeping, and was also shown to increase low-frequency electroencephalographic (EEG) activity (under 3 Hz).

2.8. Therapeutic effects

Abnormal cortical excitability is implicated in a wide range of neuropsychiatric disorders including epilepsy, depression and schizophrenia (Fitzgerald et al., 2002b; Reid et al., 2002; Saugstad, 1994; Wright et al., 2006) and preliminary studies of tDCS have investigated the application of the technique in a number of these conditions. Successful blinding with sham treatments has been shown to be feasible, thus improving study protocols for clinical trials (Gandiga et al., 2006). Since tDCS typically only induces a tingling sensation under the electrodes for the first 30–60 s of its application and then rapidly fades, sham treatment can simply be provided by inconspicuously switching the current off after 30 s of active stimulation (Gandiga et al., 2006).

Initial therapeutic applications of tDCS have focused on neurological diseases. Most studies have been only exploratory and positive effects almost exclusively await replication. For example, anodal tDCS and 10 Hz rTMS of the left temporoparietal area have each been shown to produce a transient reduction in tinnitus when compared with sham stimulation, cathodal stimulation and stimulation to other areas with rTMS or tDCS (Fregni et al., 2006c). In a double-blind, sham-controlled, crossover study, motor function as measured by the Jebsen–Taylor Hand Function Test in patients with chronic stroke was improved following tDCS and was accompanied by an increase in motor cortical excitability (Hummel et al., 2005). The effects of a single tDCS session persisted for more than 25 min after the stimulation but returned to baseline levels during repeat testing 10 days later. In another study, patients with central pain from traumatic spinal cord injury experienced significant improvement 16 days after a course of tDCS treatment to the motor cortex (Fregni et al., 2006a). The improvement occurred following 5 consecutive days of anodal (but not sham) tDCS of 2 mA and it was proposed that this may have been due to a secondary modulation of thalamic nuclei activity.

In a double-blind, sham-controlled crossover study, MEPs in patients with Parkinson's disease were increased following a single session of anodal stimulation to M1 when compared to sham stimulation, cathodal stimulation of M1, and anodal or cathodal stimulation of the DLPFC (Fregni et al., 2006d). When tested immediately after treatment, motor function was also improved in the anodal M1 condition, suggesting that tDCS may have therapeutic potential in patients with this disorder. In a randomised, sham-controlled study of 32 patients with fibromyalgia, 20 min of 2 mA anodal stimulation to M1 resulted in greater pain amelioration than sham or DLPFC stimulation. These effects were still present at 3 weeks follow-up (Fregni et al., 2006e).

To date, few trials have examined the effectiveness of tDCS in treating mental illness. Fregni et al. (2006f) conducted a randomised, controlled trial of anodal tDCS applied to left prefrontal cortex in patients with major depression. Ten patients were randomised to sham or active conditions, the latter involving five treatments administered on alternate

days. There was a significant decrease in the Hamilton Depression Rating Scale and Beck Depression Inventory scores for patients in the active but not in the sham group. This suggests potential for further trials and clinical application of tDCS in depression and other mood disorders. In a separate paradigm, a single session of anodal tDCS to left DLPFC transiently improved performance on an affective go/no-go task in a randomised trial of 26 patients with depression, suggesting that tDCS may have immediate effects on some of the information processing deficits that characterise this disorder (Boggio et al., 2007).

tDCS has also been used to investigate pathological mechanisms in other diseases. For example, anodal tDCS has been found to increase the propagation velocity of cortical spreading depression (CSD), an indicator of cortical excitability (Liebetanz et al., 2006). CSD is characterised by alterations in cerebrocortical ion homeostasis in response to the direct stimulation of brain tissue. The alterations result in a wave of neuronal excitation propagating through the cortex followed by transient inhibition. This may have relevance to the use of tDCS in patients who suffer from migraine since CSD is implicated in the mechanism underlying migrainous aura (Lauritzen, 1994). Another study found that cathodal stimulation had minimal effect on increasing TMS-induced phosphate thresholds in patients with migraine when compared with controls (Chadaide et al., 2007). This effect was particularly pronounced though in migraineurs with aura, suggesting a role of deficient cortical inhibitory processes.

2.9. tDCS, TMS priming and pharmacological modulation

As well as a stand-alone technique, tDCS may have an important role in combination with other neuromodulatory approaches. For example, it has been shown to prime the effects of rTMS and interact with the effects of various drugs.

In regard to rTMS, priming effects have been shown to occur following tDCS in a study by Lang et al. (2004a). After 10 min of anodal, cathodal or sham tDCS to left M1, a 100-stimuli train of 5 Hz rTMS was applied. Following this, MEPs in response to single-pulse TMS were measured. No effects on MEP magnitude were found in the sham tDCS condition. Preconditioning with cathodal tDCS though, which typically reduces corticospinal excitability, resulted in the subsequent 5 Hz rTMS increasing corticospinal excitability to above baseline levels. In contrast, preconditioning with anodal tDCS, which typically increases corticospinal excitability, resulted in subsequent 5 Hz rTMS reducing levels of excitability below baseline levels. A similar investigation of anodal, cathodal and sham tDCS preconditioning followed by 1 Hz rTMS found that anodal priming led to a reduction in corticospinal excitability (Siebner et al., 2004). Again, the converse applied for cathodal priming with inhibitory preconditioning resulting in 1 Hz rTMS-induced increase in corticospinal activity, contrary to its usual action on non-primed cortical areas. However, in a study of subjects with focal hand dystonia ('writer's cramp'), it was found that in contrast to healthy volunteers, pre-treatment anodal tDCS to M1 (hand) did not induce an enhancing effect on the 1 Hz rTMS-induced inhibition, and cathodal tDCS also did not result in inhibition (Quartarone et al., 2005). It was suggested that abnormal homeostatic

mechanisms may have led to the unfocused muscle contraction in the dystonia subjects.

Similar findings suggestive of the relationship of homeostatic mechanisms to preconditioning effects have been found in other studies. Repetitive electronic stimulation (ES) direct to the cortex is a technique that mimics rTMS and can alter cortical excitability as measured by CSD (Fregni et al., 2007). It has been found that when active or sham 1 Hz ES was applied to Wistar rats preconditioned with active, sham or cathodal tDCS, a pattern suggestive of homeostatic mechanisms emerged (Fregni et al., 2007). 1 Hz ES that was applied alone or was preceded by cathodal tDCS, reduced CSD velocity whereas anodal tDCS followed by 1 Hz ES increased CSD velocity. Homeostatic effects have also been found in the effects of tDCS on paired associative stimulation (PAS) of human motor cortex. When applied before PAS, anodal tDCS boosted its effects whereas cathodal preconditioning resulted in inhibition (Nitsche et al., 2007b). However, when applied simultaneously, the reduced background activity resulting from cathodal tDCS increased the effects from PAS while the converse occurred for anodal stimulation. The results of these studies suggest that the observed preconditioning effects may stem from a homeostatic mechanism in the human motor cortex for stabilising excitability within an appropriate physiological range. It remains to be investigated whether similar homeostatic mechanisms are present in non-motor cortical areas. This seemingly homeostatic interaction between the two stimulation methods is theoretically interesting but may undermine attempts to combine tDCS and rTMS to achieve additive therapeutic effects.

Pharmaceutical modulation of the effects of tDCS present an opportunity for increasing the level of precision with which particular cortical structures can be targeted with the technique as well as enhancing our understanding of the mechanism of tDCS effects. Carbamazepine, a sodium channel blocker, and flunarizine, a calcium channel blocker, eliminate the short- and long-term effects of anodal stimulation. However, as cathode-induced changes are not affected, concurrent medication administration may enhance the likelihood of the induction of only a cathodally mediated reduction in excitability (Liebetanz et al., 2002; Nitsche et al., 2003). Through its effects on the dopamine D2 (and D1) receptor, pergolide has been shown to extend the effect of cathodal stimulation until the morning after the treatment (Nitsche et al., 2006). Similarly, administering L-DOPA, a dopamine precursor, alters the effects of anodal tDCS into inhibition, prolongs the cathodal tDCS-induced excitability diminution and extends the effects of PAS. These aftereffects are prolonged by a factor of about 20 (Kuo et al., 2007). Somewhat in contrast, lorazepam, a GABA-receptor agonist, leads to an initially delayed but then enhanced and prolonged effect of anodal-induced excitability elevation (Nitsche et al., 2004b) and D-cycloserine, a partial NMDA-receptor agonist, selectively potentiates the duration of motor cortical excitability enhancements resulting from anodal tDCS (Nitsche et al., 2004c). Amphetamine administration also enhances anodal-induced excitability, particularly the long-term changes (Nitsche et al., 2004d). These studies suggest that the therapeutic efficacy of anodal tDCS could be enhanced by the co-administration of lorazepam, D-cycloserine or amphetamine,

while the cathodal aspects of a treatment could be isolated and enhanced by concurrently giving carbamazepine or flunarizine with pergolide. Further pharmacological manipulations of tDCS effects could also be investigated in future studies, particularly if the technique becomes more widely used as a therapeutic tool.

2.10. Summary

The potential of tDCS as a neurostimulation intervention has not yet been fully realized. However, its role in affecting cortical excitability, along with the possibility of targeting and modulating its effects by combining it with rTMS and pharmaceutical interventions, suggest this method has considerable potential as a non-invasive tool in a range of investigative and clinical studies.

3. Caloric vestibular stimulation

3.1. Background

Caloric vestibular stimulation (CVS) has been widely used in the neurodiagnostic context to assess vestibular function in conscious subjects and brainstem function in comatose patients (Fife et al., 2000; Wijdicks, 2001). First developed by Bárány (1906) in the early 20th century, CVS has since been the subject of substantial investigation with respect to its underlying peripheral and central neurophysiology. In recent decades, understanding of the functional neuroanatomic contributions to vestibular information processing has substantially progressed. Thus, for example, experiments employing magnetoencephalography (Hegemann et al., 2003; Nishiike et al., 2002), cortical electrostimulation (Blanke et al., 2000; Kahane et al., 2003), evoked potentials (de Waele et al., 2001; Schneider et al., 2001), and post-lesional assessment of vestibular function (Cereda et al., 2002; Hegemann et al., 2004; Israël et al., 1995; Papathanasiou et al., 2006; Philbeck et al., 2006; Ventre-Dominey et al., 1999; Urasaki and Yokota, 2006) have identified a broad network of vestibular processing brain regions that have also been found to be activated by CVS. This network has been considered the human homologue of a multimodal (polysensory) vestibular cortical system in monkeys (reviewed in Barmack, 2003; Brandt and Dieterich, 1999; Dieterich and Brandt, 2000; Fukushima, 1997; Guldin and Grüsser, 1998).

CVS is one of a number of related techniques that have been shown to induce brain activation in this multimodal network. Others include galvanic and rotational vestibular stimulation (GVS and RVS, respectively), neck muscle vibration (NMV; via proprioceptors) and optokinetic stimulation (OKS; via visual stimulation). Along with demonstrations of brain activations induced by these related techniques, striking phenomenological effects associated with such activations, especially as induced by CVS, have also been reported. These phenomenological effects have been studied in a wide range of contexts within the cognitive and clinical neurosciences. They suggest that like tDCS, CVS has the potential to be a highly useful neurostimulation technique. Despite this promise, CVS (and related techniques) has as yet not been utilized

widely as a clinical tool. This in part reflects the preliminary nature of the clinical research and perhaps the lack of financial drive to develop a technique that has not been commercialized.

3.2. Experimental technique and safety

The caloric stimulation procedure (Fig. 1A) involves irrigation of the external auditory canal with cold or warm water (or air). It has traditionally been believed to achieve its effects by inducing a temperature change across the semicircular canals, thus altering the density of the endolymphatic fluid (Bárány, 1906). This creates convection currents that cause cupular deflection, leading to stimulation of the vestibular nerve and vestibular nuclei with elicitation of the vestibulo-ocular reflex and resultant nystagmus. This view of the peripheral mechanism of action of CVS has been questioned with evidence suggesting that a non-thermoconvective current component may also play a role (Scherer et al., 1986), however this issue is beyond the scope of the present review. Regardless of its peripheral mechanism of action, CVS results in a brisk phase of nystagmus with the direction contralateral to the ear irrigated following cold-water irrigation, and with an ipsilateral direction following warm-water irrigation. More importantly with respect to the present review, warm-water irrigation induces ipsilateral hemispheric activation whereas cold water leads to contralateral activation (see below).

A typical CVS protocol involves irrigation of the auditory canal with 50 ml of most commonly cold (iced) water for 30 to 60 s, using a syringe with a piece of soft silastic tubing attached. The end of the tubing is placed close to the tympanic membrane. Nystagmus and a subjective report of vertigo usually occur rapidly and continue for several minutes. The procedure infrequently may cause mild nausea, a mild headache and rarely vomiting. It is otherwise a safe and non-invasive technique that is well tolerated in the majority of subjects. The CVS method and additional safety considerations are discussed further in the caption to Fig. 1.

3.3. Brain imaging studies

Earlier studies measuring EEG patterns during CVS (herewith 'CVS' indicates cold-water stimulation, unless otherwise specified) have suggested greater hemispheric activation contralateral to the side of irrigation (e.g., Barac, 1967). More recently, PET and functional MRI (fMRI) studies have been more informative in identifying the neural structures activated following CVS. These areas include temporal-parietal cortex (superior temporal gyrus, inferior parietal lobe, and temporal-parietal junction), anterior cingulate cortex (ACC), insular cortex, and putamen in the basal ganglia (Bottini et al., 1994, 1995, 2001; Emri et al., 2003; Kisely et al., 2002; Tuohimaa et al., 1983; Vitte et al., 1996; Wenzel et al., 1996; Fig. 1A). Along with temporoparietal and insular cortical areas, other CVS-activated regions such as somatosensory area SII and the parietal operculum have also been regarded as representing the human homologue of monkey parietoinsular vestibular cortex, the core region of the multimodal network (as mentioned above; Bottini et al., 1995, 2001; Blanke et al., 2000; Duque-Parra, 2004; Eickhoff et al., 2006; Kahane et al., 2003; Petit and Beauchamp, 2003).

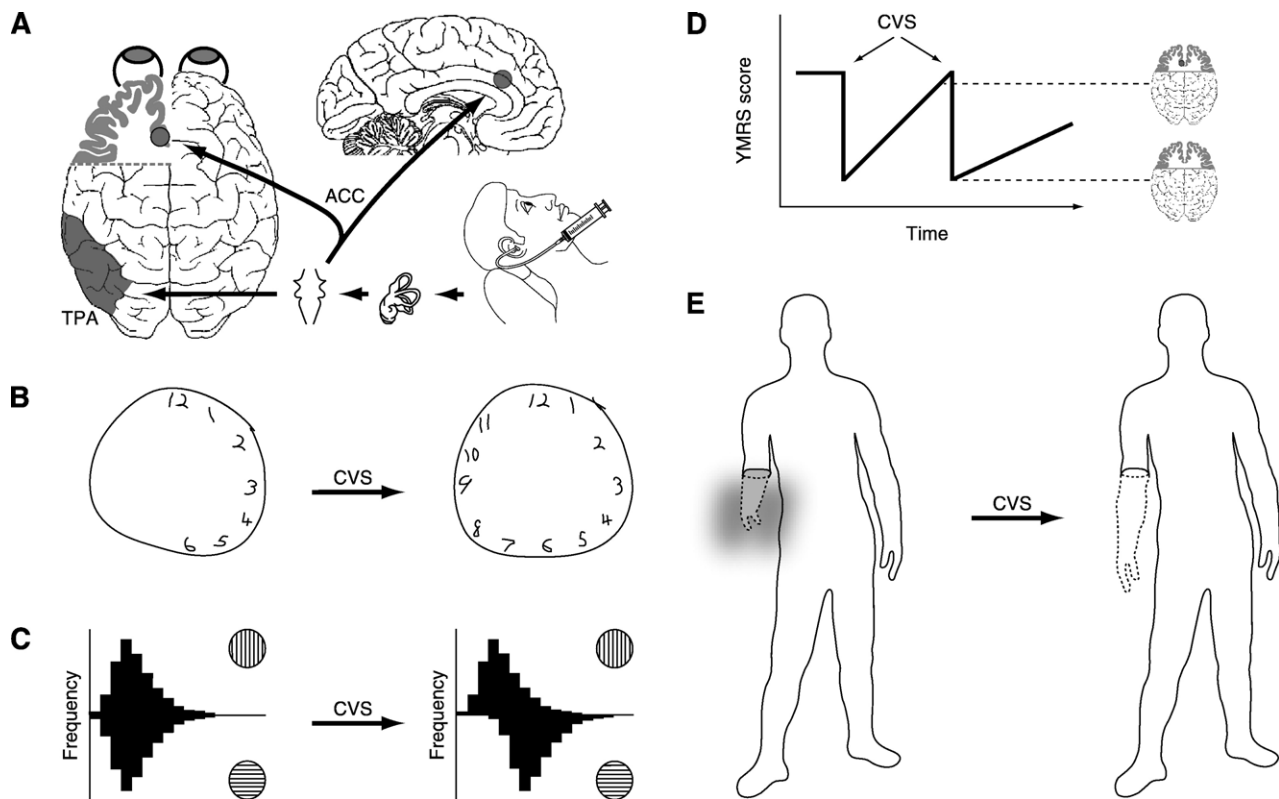


Fig. 1 – The CVS procedure and some of its demonstrated effects. (A) Right-ear CVS with cold water activates, through the semicircular canals and vestibular nuclei, brain regions in the contralateral hemisphere such as the anterior cingulate cortex (ACC) and temporoparietal areas (TPA; activation of other areas such as insular cortex and the putamen in the basal ganglia are not indicated). (B) One pencil-and-paper test used to detect (left) unilateral neglect involves the patient being instructed to draw a complete symmetrical clock face. Patients with the disorder fill in numbers on the right side only (as depicted, despite having drawn a whole circle) or may include more digits on the right than the left side. Following CVS of the left ear (i.e., activation of the lesioned right hemisphere), subjects' left-sided attentional neglect is temporarily ameliorated for 10–15 min (Vallar et al., 1997; Rossetti and Rode, 2002) as represented by the subsequent drawing of a complete clock face. (C) The schematic BR interval duration frequency histograms represent the time an observer perceives one image (e.g., vertical lines) relative to the other (e.g., horizontal lines) within a given viewing period. Before CVS, the vertical and horizontal gratings are perceptually dominant for a roughly similar duration. Following CVS, predominance of horizontal image perception increases, reflected in the higher frequency of longer horizontal interval durations (see Miller et al., 2000). (D) According to Pettigrew and Miller's (1998) pathophysiological model of bipolar disorder, left-ear CVS (right-hemisphere activation) restores toward normal the disordered left-over-right hemispheric activation asymmetry associated with mania (Blumberg et al., 2000). This specific prediction was assessed and verified in a case study by Dodson (2004; see main text). The graph represents the effects of CVS on the patient's YMRS score. (E) In patients experiencing phantom limb following amputation, CVS has been reported to restore abnormal phantoms (e.g., telescoped phantoms, as depicted in left figure) to normal phantoms, and painful phantoms to non-painful phantoms (André et al., 2001).

CVS administration: In our use of the CVS technique, subjects are screened by a medical practitioner to determine suitability for participation. Exclusion criteria we have used (which will obviously vary depending on the study, in particular the clinical group under investigation) include the following: (i) a diagnosis or family history of an axis I psychiatric disorder; (ii) epilepsy or any brain disorder such as a brain injury, tumor or other significant neurological disease; (iii) significant cardiac or respiratory disease; (iv) ear disease such as a perforated ear drum or otitis media/externa; (v) vestibular disease or significant motion sickness and (vi) pregnancy. Written informed consent is obtained. Subjects are otoscopically examined by the medical practitioner for any signs of significant ear disease. The subject lies on a couch maintaining a vertical midsagittal plane, with head orientation kept at 30° from the horizontal plane. Iced water is irrigated into the external auditory canal using a 50-ml plastic syringe with a short piece of soft silastic tubing attached (the silastic tubing is readily available from intravenous cannulas, with the needle end removed). The end of the tubing is positioned near but not touching the tympanic membrane. Irrigation continues until there are demonstrable signs of nystagmus and reports of vertigo. The reflux water is collected in a kidney dish placed on the subject's shoulder. In the authors' (T.T.N. and S.M.M.) experience of administering CVS to several hundred subjects, only three subjects requested that CVS be ceased (as a result of cold-related discomfort). Many find the experience of vertigo interesting. A mild headache may follow CVS (easily relieved with simple analgesics), as may mild nausea. Rarely vomiting may occur (in only two of our test subjects out of several hundred). Sham stimulation can be administered by irrigating the ear canal with water at body temperature (which does not induce vestibular stimulation); however, the lack of vertigo may suggest to the subject that actual stimulation has not occurred. Figure and caption from Miller and Ngo (2007; Wiley-Blackwell Publishing) reprinted with permission.

An earlier SPECT (single-photon emission computed tomography) investigation that used cold-air stimulation of the right ear found greater increases in activity in the left superior parietal lobe relative to that on the right (Takeda et al., 1996). Naito et al. (2003) in a recent PET study analysed scans of cold-air stimulation in one ear combined with scans of hot-air stimulation in the opposite ear (from a different subject group) and found unilateral activation of the inferior parietal and insular regions. These results are consistent with the above PET and fMRI studies demonstrating CVS-induced activation of regions in the contralateral hemisphere with cold stimulation and in the ipsilateral hemisphere with warm stimulation. Bense et al. (2003a) used PET to examine left-ear cold CVS and reported contralateral activation in temporoparietal areas. These investigators have also examined the effects of warm-water CVS, including assessment of the effect of handedness. They reported relatively greater activation ipsilateral to the side of stimulation (Dieterich et al., 2003a), consistent with other studies. In addition, they found that this ipsilateral activation occurred to a greater extent when in the non-dominant hemisphere (e.g., the activation in the right hemisphere in right-handers following right-ear warm CVS was greater than that seen in the left hemisphere of right-handers following left-ear warm CVS; see also Lobel et al., 1996). These investigators (Dieterich et al., 2003a, 2005a) thus proposed a right hemispheric dominance for cortical vestibular processing that was critically involved in a larger right-dominant network for visuospatial representation, oculomotor control, gravity perception and posture control (see also Jahn et al., 2004).

Other studies examining cold CVS with fMRI have also found a tendency towards a greater magnitude of contralateral activation in the non-dominant hemisphere in right-handers (Fasold et al., 2002; Suzuki et al., 2001; see also Fink et al., 2003; Eickhoff et al., 2006, for similar fMRI findings following GVS). It is important to note that despite this evidence for greater non-dominant hemisphere activations in right-handers, the pattern of cold-contralateral and warm-ipsilateral activation is nevertheless generally found across all the brain-imaging studies. Along with CVS, other techniques such as GVS, NMV and OKS have also been shown to activate temporoparietal and insular regions (reviewed in Karnath and Dieterich, 2006). All except CVS, however, have not been found to consistently activate ACC and the putamen (Bottini et al., 1994, 1995, 2001; Bense et al., 2001, 2005, 2006; Bucher et al., 1997, 1998; Dieterich et al., 1998, 2003b; Fink et al., 2003; Galati et al., 1999; Lobel et al., 1998; Stephan et al., 2005; Wenzel et al., 1996). In addition, CVS and GVS have been shown to induce deactivation of striate, extrastriate and frontal areas bilaterally (Bottini et al., 2001; Wenzel et al., 1996; Bense et al., 2001; Stephan et al., 2005). The subcortical-to-cortical pathways involved in mediating the above patterns of brain activation have also recently been under investigation (Bense et al., 2003b, 2004; Dieterich et al., 2005a,b).

3.4. Effects on vision and cognition

Brain-imaging demonstrations of unilateral hemispheric activation following CVS, particularly of structures known to be involved in attentional processing, led to the use of CVS to investigate the neural mechanisms of a visual phenomenon –

binocular rivalry (BR). BR occurs when two different stimuli are presented simultaneously, one to each eye. The brain deals with this conflicting sensory input by perceiving each image in alternation, every few seconds. CVS was applied during BR and was shown to affect the perceptual predominance of the rivaling images (Miller et al., 2000; Miller, 2001; Ngo et al., 2007; Miller and Ngo, 2007; Fig. 1C). CVS has also been shown to affect perceptual predominance of the two perspectives of the Necker cube, a related form of perceptual rivalry (Miller et al., 2000), as well as Rubin's vase–faces illusion (Ngo et al., *in press*). In yet another rivalry context, CVS was applied to interocular grouping during BR and was shown to affect the predominance of grouped but not the non-grouped percepts (Ngo et al., 2007). The use of CVS in these contexts has led to novel mechanistic models of rivalry based on alternating unihemispheric attentional selection (interhemispheric switching). In all of these perceptual rivalry experiments, only right-ear CVS caused significant predominance changes, with left-ear CVS having no significant effect. This asymmetry was interpreted based on hemispheric asymmetries of both BR (Lumer et al., 1998) and spatial representation (Heilman and Van Den Abell, 1980).

In addition to these documented effects of CVS on perceptual rivalry, the technique has also been employed in visual imagery tasks. An earlier study showed that left- or right-ear CVS did not influence subjects' accuracy and reaction time of verbal recall of characters from the imaginal left- or right-half of a grid (Alway et al., 1994; the investigators raised a number of methodological factors that could have partly accounted for the negative findings). More recently though, Mast et al. (2006) demonstrated that left-hemisphere activation via simultaneous left-ear warm CVS and right-ear cold CVS significantly impaired subjects' performance in the mental rotation of letters and in a detailed visual imagery task (but not in a control task of similar difficulty that did not involve visual imagery). While the bilateral stimulation employed in that study may have induced greater unihemispheric activation than either unilateral stimulation alone (as used by Alway et al., 1994), the effect of these and a range of other CVS methodological factors remain to be specifically examined (Miller and Ngo, 2007). Nevertheless, concordant with the findings of Mast et al. (2006), it was also recently found that TMS-induced disruption of the right temporoparietal junction (an area activated by CVS) significantly impaired subjects' imaginal changes in body position and visual perspective (Blanke et al., 2005). In this context, it is also interesting to note that TMS of the temporoparietal cortex disrupts BR (Miller et al., 2000).

Despite brain-imaging studies consistently demonstrating unihemispheric activation following CVS, laterality researchers have yet to fully exploit the hemisphere-specific activation induced by the technique. In one exception, Bächtold et al. (2001) found spatial memory in healthy subjects improved following left-ear CVS (right-hemisphere activation) while verbal memory improved following right-ear CVS (left-hemisphere activation). This suggests that the CVS-induced contralateral activation is neural activation per se, rather than activation of contralateral inhibitory circuits.

In other perceptual contexts, Lewald and Karnath (2000) presented dichotic noise (perceived as a single sound image) and

required subjects to adjust the difference in sound level between the ears such that the auditory percept stayed in the median plane of the head. Compared with the control condition (stimulation with 37 °C water), CVS shifted the perception of the sound image contralaterally, indicated by subjects significantly increasing the sound level towards the irrigated side to re-centre the auditory percept. This finding was corroborated in similar studies using whole-body tilt (Lewald and Karnath, 2002), NMV (Lewald et al., 1999) and RVS (Lewald and Karnath, 2001), wherein the latter two also induced the sound image to be displaced towards the activated hemisphere, although the size of this lateralised effect was much greater following CVS than RVS.

These and other experiments using CVS have investigated the effect of stimulation on spatial representation and related functions, in an effort to understand the processes that may underlie pathological neglect (see below). Thus, CVS has been found to induce a range of effects in this context, including the following (in relation to side of irrigation): (i) ipsilaterally shifting subjective perception of the body orientation's mid-sagittal plane (associated with the apparent contralateral movement of a stationary visual target and with ipsilateral ocular exploration of space; Karnath, 1994; Karnath et al., 1994, 1996; cf. Richard et al., 2001); (ii) increasing (erroneous) pointing towards the irrigated side in locating a memorized visual target (Schmäl et al., 2000; cf. Schmäl et al., 2005); (iii) evoking ipsilateral ocular exploration of space (Karnath et al., 1996); and (iv) shifting spontaneous (cf. goal-directed) tactile exploration and spontaneous head orientation towards the stimulated side (Karnath et al., 2003).

3.5. Effects on neglect and other post-lesional conditions

Temporary resolution of post-stroke neglect with CVS is a recognized and well-replicated phenomenon (e.g., Adair et al., 2003; Geminiani and Bottini, 1992; Rode and Perenin, 1994; Schiff and Pulver, 1999; Fig. 1B). Usually these CVS effects begin within 30 s following the irrigation, with the improvement lasting around 10–15 min (Rossetti and Rode, 2002). An earlier study by Rubens (1985) found that left-ear cold CVS or right-ear warm CVS, in a group of right-hemisphere lesion patients, temporarily alleviated their left-sided attentional neglect. More recently in a single case study of a right-hemisphere brain-damaged patient, bilateral cold CVS did not improve neglect whereas left-ear stimulation improved it and right-ear stimulation worsened it (Rode et al., 2002). These direction-specific effects clearly argue against the notion of an arousal interpretation of CVS effects (i.e., that it is merely the general arousal from the cold-water irrigation that induces the effects of CVS as opposed to region-specific activation). In a separate case study of a right-hemisphere stroke patient, EEG analysis during the temporary remission of neglect following a single administration of left-ear cold CVS showed bilateral increased hemispheric activation but with greater activation on the right than the left side (Storrie-Baker et al., 1997), again supporting the notion of contralateral activation.

Consistent with the brain-imaging studies of CVS, unilateral attentional neglect can occur following lesions to any of the reported contralateral brain regions activated by CVS (i.e., temporoparietal cortex, insular cortex, anterior cingulate cortex and putamen in the basal ganglia; almost always on

the right side; Karnath et al., 2002, 2004, 2005; Leibovitch et al., 1998, 1999). Although less common than left-sided neglect following right-hemisphere lesions (Bowen et al., 1999; Heilman and Van Den Abell, 1980), right-sided neglect following left-hemisphere lesions has similarly been found to be ameliorated with CVS (of the right ear). This was demonstrated in a patient with a left-sided lesion who also had severe dysphasia, and notably only the right-sided neglect improved following right-ear CVS with no improvement in the dysphasia (Vallar et al., 1995a).

The post-lesional conditions in which CVS has demonstrated temporary symptomatic alleviation are not limited to neglect phenomena. Thus, for example, consistent with earlier findings (Vallar et al., 1990), it has recently been shown that hemianaesthesia was ameliorated following a single session of left-ear CVS (Bottini et al., 2005). In addition, anosognosia (unawareness or denial of deficits such as contralesional paralysis) can also be ameliorated for 15 min to 24 hr following left-ear CVS (Cappa et al., 1987; Ramachandran, 1994; Rode et al., 1992, 1998; Vallar et al., 1990). Similarly, left-ear CVS has been found to significantly alleviate deficits in spontaneous movement (i.e., motor neglect) and to improve strength contralesionally for up to 20 min in right-hemisphere lesion patients, about half of whom also had their anosognosia and attentional neglect temporarily ameliorated by the intervention (Rode et al., 1998). In the same study, right-sided motor deficits in left-hemisphere lesion patients were not alleviated following right-ear CVS, again arguing for the notion of region-specific (lateralized) effects of CVS. Finally, in right-hemisphere lesioned patients with somatoparaphrenia (bizarre beliefs regarding their left hemiplegic limbs, e.g., that they belong to someone else or reside elsewhere), left-ear CVS has been shown to ameliorate such delusions for up to 2 h (Bisiach et al., 1991; Rode et al., 1992).

The above CVS studies of neglect and related phenomena have demonstrated temporary therapeutic improvements but have not assessed for sustained therapeutic effects following repeated stimulations. However, it has been demonstrated that repeated stimulation sessions using NMV in the post-stroke context does indeed induce sustained amelioration of neglect. As occurs with CVS, temporary ameliorating effects on post-lesional attentional neglect also occurs with NMV, GVS, RVS and OKS (Karnath, 1994; Karnath et al., 1993, 1996; Kerkhoff et al., 2006; Mattingley et al., 1994; Pizzamiglio et al., 1990; Rorsman et al., 1999; Schindler and Kerkhoff, 2004; Vallar et al., 1995b; see also below). In the repeated-NMV study, the stimulation was administered over 5 sessions per week for 3 weeks, with the resulting neglect amelioration lasting for up to 2 months. In this study, NMV in combination with standard visual exploration training produced better attention-related outcomes than standard exploration training alone (Schindler et al., 2002). Moreover, multiple NMV sessions in the absence of standard treatments have also been reported to induce similar sustained therapeutic effects (Johannsen et al., 2003).

3.6. Effects on mood disorders

EEG, TMS, post-stroke and cognitive studies have suggested an association of affective disorders with hemispheric activation asymmetries with typically greater relative activation of the

left hemisphere in mania and greater relative activation of the right hemisphere in depression (discussed in Pettigrew and Miller, 1998). In addition, there is recent evidence of hypoactivity of the right vestibular nuclei in patients with depression (Soza Ried and Aviles, 2007), a finding that is consistent with the notion of greater relative right-hemisphere activation when taking into account the crossed projections of the vestibular nuclei (Barmack, 2003). The findings of hemispheric activation asymmetries in mania and depression and observations of altered BR in bipolar disorder (Miller et al., 2003) were utilized by Pettigrew and Miller (1998) who proposed a pathophysiological model of bipolar disorder which predicted potential hemisphere-specific therapeutic effects of CVS in mania and depression (with left-ear/right-hemisphere CVS predicted to reduce the signs and symptoms of mania and right-ear/left-hemisphere CVS predicted to reduce the signs and symptoms of depression) (Miller and Ngo, 2007). Although this has not been tested in a randomised trial to date, it is partially supported by an interesting case report. Dodson (2004) treated a 29-year-old woman with a 10-year history of bipolar disorder who had been admitted with an acute manic episode of several weeks in duration. Her symptoms did not respond to an increased dose of medication, or to five ECT treatments for which she withdrew consent after there was no improvement. She also became intolerant of pharmacotherapy. As an alternative, a therapeutic trial of left-ear cold-water CVS was performed (Fig. 1D). Following the CVS procedure, the patient showed dramatic improvement with her Young Mania Rating Scale score decreasing from 32 at pre-stimulation to 10 at 10 min post-stimulation. There followed a gradual increase in her symptoms over the next 72 h at which point CVS was performed again with a similar therapeutic benefit and the effects also seemed to be longer-lasting. No further follow-up was reported but clearly, this case study suggests that further investigation of potential sustained therapeutic benefits of left-ear CVS in mania, and assessment of right-ear CVS in depression, is warranted.

3.7. Effects on pain disorders

The potential clinical benefits of repeated CVS are not limited to post-lesional and mood disorders. Indeed, CVS has also been shown to temporarily ameliorate pain in several chronic pain conditions, raising the issue of potential pain management benefits with the technique (Miller and Ngo, 2007). For example, of 10 subjects with phantom limb pain, all 10 reported that CVS improved their pain and several subjects reported that abnormal phantoms were experienced as normal phantoms following the intervention (André et al., 2001; Fig. 1E). It was postulated that CVS restored somatosensory representation (the global body schema) to normal. In another chronic pain context, 2 of 4 subjects with pain following spinal cord injury reported that CVS greatly reduced their pain (Le Chapelain et al., 2001). Moreover, pain following CVS was also reportedly diminished in a patient with complex regional pain syndrome (Williams and Ramachandran, 2006). Of particular interest with respect to potential clinical utility, it was recently reported that a single session of CVS induced sustained amelioration of pain (for up to several weeks at least)

associated with post-stroke thalamic pain syndrome (Ramachandran et al., 2007). This finding was all the more remarkable given that the pain in the two patients studied had existed for years and was refractory to multiple interventions. In no chronic pain context has CVS been administered repeatedly to assess for pain management benefit. Along with future clinical trials suggested by this evidence for CVS effects on chronic pain, investigations of the mechanisms of pain perception and attitudes toward pain (including comorbid mood disorders) could also utilize CVS in exploratory studies.

3.8. Summary

CVS is a safe, non-invasive and inexpensive means of achieving region-specific unilateral hemispheric activation. It thus presents as a highly useful brain stimulation technique for investigating a variety of visual and cognitive phenomena as well as clinical conditions such as post-lesional disorders, affective disorders and chronic pain conditions. However, clinical trials for therapeutic utility are lacking despite suggestions of potential therapeutic effects. Considerable further work on these issues is therefore required.

4. Overall summary

tDCS and CVS are safe brain stimulation techniques that can be used to examine a variety of phenomena of interest to cognitive neuroscience. Furthermore, these techniques have demonstrated effects in a range of clinical conditions and may have therapeutic potential in such disorders. The ability of tDCS and CVS to selectively modulate cortical excitability and induce relative unihemispheric activation, respectively, becomes useful as we further understand the neural abnormalities in the disorders in which these techniques have been shown to exert effects. Both tDCS and CVS appear to be relatively free of side effects and are considerably cheaper than techniques such as rTMS and ECT. While the extent of the utility of tDCS and CVS in these and other contexts requires further investigation, they are likely to become valuable additions to the current armamentarium of neurostimulation techniques available to researchers of brain function and dysfunction.

Acknowledgments

We thank the anonymous reviewers for helpful comments on an earlier version of the manuscript. P.B.F. was supported by a Practitioner Fellowship from the National Health and Medical Research Council of Australia and by a NARSAD Young Investigator Award.

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