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Reviews and perspectives

Electrified minds: Transcranial direct current stimulation (tDCS) and Galvanic Vestibular Stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology—A review of current data and future implications

Kathrin S. Utz[a,c,*], Violeta Dimova[a,c], Karin Oppenländer[b], Georg Kerkhoff[a,c,*]

[a] Clinical Neuropsychology Unit, Saarland University, Saarbruecken, Germany
[b] Neurological Clinic Bad Aibling, Germany
[c] International Research Training Group 1457 "Adaptive Minds", Saarbruecken, Germany

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ABSTRACT

Transcranial direct current stimulation (tDCS) is a noninvasive, low-cost and easy-to-use technique that can be applied to modify cerebral excitability. This is achieved by weak direct currents to shift the resting potential of cortical neurons. These currents are applied by attaching two electrodes (usually one anode and one cathode) to distinct areas of the skull. Galvanic Vestibular Stimulation (GVS) is a variant of tDCS where the electrodes are attached to the mastoids behind the ears in order to stimulate the vestibular system. tDCS and GVS are safe when standard procedures are used. We describe the basic physiological mechanisms and application of these procedures. We also review current data on the effects of tDCS and GVS in healthy subjects as well as clinical populations. Significant effects of such stimulation have been reported for motor, visual, somatosensory, attentional, vestibular and cognitive/emotional function as well as for a range of neurological and psychiatric disorders. Moreover, both techniques may induce neuroplastic changes which make them promising techniques in the field of neurorehabilitation. A number of open research questions that could be addressed with tDCS or GVS are formulated in the domains of sensory and motor processing, spatial and nonspatial attention including neglect, spatial cognition and body cognition disorders, as well as novel treatments for various neuropsychological disorders. We conclude that the literature suggests that tDCS and GVS are exciting and easily applicable research tools for neuropsychological as well as clinical-therapeutic investigations.

Contents

Abbreviations: tDCS, transcranial direct current stimulation; GVS, Galvanic Vestibular Stimulation; DC, direct current; TMS, transcranial magnetic stimulation; fMRI, functional magnetic resonance imaging; PET, Positron Emission Tomography; CVS, caloric vestibular stimulation; MEP, motor evoked potentials; EMG, electromyogram; DLPFC, dorsolateral prefrontal cortex; M1, primary motor cortex; mA, milliAmpere; SEPs, somatosensory evoked potentials.

* Corresponding authors at: Clinical Neuropsychology Unit, Department of Psychology, Saarland University, P.O. Box 151150, D-66041 Saarbruecken, Germany. Tel.: +49 681 302 57385/57380; fax: +49 681 302 57382.
E-mail addresses: k.utz@mx.uni-saarland.de (K.S. Utz), kerkhoff@mx.uni-saarland.de (G. Kerkhoff).

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1. Introduction

Neuropsychology has enormously benefited from the advent of modern neuroimaging techniques such as functional magnetic reasonance imaging (fMRI), recording of event-related potentials (ERPs) and brain stimulation techniques such as transcranial magnetic stimulation (TMS; Wasserman, Epstein, & Ziemann, 2008). Recently, a number of novel brain stimulation techniques have become increasingly popular, including deep brain stimulation, magnetic seizure therapy and vagus nerve stimulation (Been, Ngo, Miller, & Fitzgerald, 2007; Eitan & Lerer, 2006). A serious drawback of these methods is the fact that all except TMS are invasive and expensive to administer. TMS has been used to study the excitability of the cortex, cortical regional connectivity, the plasticity of brain responses and cognitive processes in healthy subjects and the functional deficits underlying psychiatric disorders such as depression (Been et al., 2007). As a result of advances in brain imaging our knowledge of relevant brain regions which should be targeted to induce changes in motor, sensory, cognitive or emotional functions has greatly increased in the last two decades. Consequently, techniques of neurostimulation that are easier to use and less expensive than TMS might further broaden our understanding of neuropsychological functions both in normal and clinical subjects. A very promising method is transcranial direct current stimulation (tDCS). tDCS offers the possibility of changing cortical excitability and this can be achieved by the application of electrodes with different polarity to different locations on the surface of the skull to excite the underlying neural tissue. A variant of this method is Galvanic Vestibular Stimulation (GVS) where the vestibular system is stimulated by attaching two electrodes to the mastoids behind the ears. GVS does not only induce electrical activation in peripheral vestibular afferents but also affects different cortical-vestibular areas and neighbouring cortical regions. Both techniques are non-invasive, safe, inexpensive and without serious adverse effects when certain standards are maintained. Moreover, tDCS does not only produce *online-effects during* the application but can induce significant *aftereffects* (Nitsche & Paulus, 2001) depending on the duration of stimulation. This makes tDCS an attractive tool for researchers interested in learning, neuroplasticity and neurorehabilitation. Finally, in comparison with TMS both tDCS and GVS are less expensive, easy to administer and without serious adverse effects.

This review describes the basic physiological principles of tDCS and GVS, addresses issues of safety and usability, and then assesses the state of the art of these techniques when used in different neuropsychological domains. Additionally, we will suggest novel and potentially fruitful applications of both techniques in a number of research fields, including spatial neglect, spatial and non-spatial attentional processing as well as spatial-cognitive and body-cognition disorders. Finally, we will conclude with a brief discussion of the findings, a description of the main conclusions and an outlook on future directions of these exciting methods in neuropsychology. Although covering a great deal of relevant literature the current review is not intended as an exhaustive and systematic review of *all* available studies in the field. In selecting the studies we searched international journals and the PubMed database. Our main intention in this review is to present particularly illustrative examples of the potential applications of tDCS and GVS in a broad range of topics including perception, sensory, motor, cognitive and emotional processes as well as a limited range of clinical disturbances relevant for researchers and clinicians in the field of neuropsychology. We hope that the variety of applications and findings presented here in so diverse fields of neuropsychology attracts researchers and alerts them about the considerable potential of tDCS and GVS to answer important research questions in the fields of neuropsychology, neuroplasticity and neurotechnology. We did not consider single cases and non-English studies.

2. Procedure for tDCS

2.1. History

tDCS is a non-invasive method for modulating cortical excitability that has a long history. The first records of electrical therapy date back to 43–48 AD when the roman physician, Scribonius Largus, reported on the treatment of pain by electric fish. Other milestones were Galvani's[1] (1791) and Volta's (1792) experiments on animal and human electricity which initiated the clinical application of direct current stimulation in 1804, when Aldini successfully treated melancholic patients with this technique. The discovery of electroconvulsive therapy by Bini and Cerletti in the 1930s, however, led to an abrupt loss of interest in the technique of tDCS. In the 1960s this method had a brief comeback and its effects were systematically investigated. During that time it could already been shown that tDCS is able to affect brain functions *via* modulation of cortical excitability (Albert, 1966a, 1966b). In two papers that appeared 1966 in the fourth issue of NEUROPSYCHOLOGIA D.J. Albert showed that electrical (cathodal) stimulation of the rat's medial cortex abolished retention (Albert, 1966a) and anodal stimulation speeded

[1] Galvani lent his name for the later coined term Galvanic stimulation, see Section 3.

up memory consolidation (Albert, 1966b). Despite this temporary interest, the technique of tDCS was abandoned once again because of the progress made in the treatment of psychiatric disorders by drugs (for a detailed historical review see Priori, 2003).

Perhaps, a deeper insight into the basic mechanisms of tDCS was fundamental for the increased popularity of this method during recent years. This improved understanding was most likely facilitated by the study of brain mechanisms *via* new techniques such as TMS (Wasserman et al., 2008), and functional brain imaging (fMRI) and resulted in the development of clinical applications. Another important milestone was the development of safety standards, together with evidence of a lack of serious adverse effects. This makes tDCS a promising method to study the effects of local brain stimulation on cognitive functions – both in healthy subjects and patients with central nervous system lesions. In the following, a detailed description of tDCS is given including aspects of safety.

2.2. Method

tDCS consists of applying direct current over the scalp – usually delivered by a small battery-driven constant current stimulator – by attaching electrodes of different polarities to the skin (Iyer et al., 2005; Nitsche & Paulus, 2000, 2001). The electrodes should be made of conductive rubber and be put in saline-soaked synthetic sponges to prevent chemical reactions at the contact point between electrode and skin (Nitsche, Liebetanz, 2003). Concerning the ideal size of the electrodes there is no consensus. Most of the electrodes used in human studies have a size of 25–35 cm^2, which results in a current density of 0.03–0.08 milliAmpere (mA)/cm^2 when used with a current of 1–2 mA. In order to focus the effects of the electrode over the stimulation area some authors recommend a smaller electrode size. Alternatively, an enlargement of the other electrode makes this electrode functionally less active and enhances the selectivity of the other electrode (Nitsche et al., 2007).

2.3. Positioning of the electrodes

The position of the electrodes is of crucial significance for the spatial distribution *and* direction of the flow of current which together determine the effectiveness of the stimulation. In most of the tDCS studies one anode and one cathode is placed in different positions on the scalp skin, depending on the brain function under study. But other montages such as one anode and two cathodes (Miranda, Lomarev, & Hallett, 2006) or two anodes and two cathodes (Ferrucci, Mameli, et al., 2008) have also been used. For some research questions it may be more advisable to place one electrode on an extra-cephalic position (e.g. the right upper arm; Cogiamanian, Marceglia, Ardolino, Barbieri, & Priori, 2007). This may resolve the ambiguity in the interpretation of the tDCS effects with two cephalic electrodes. On the other hand, increasing the distance between the electrodes leads to an enhancement of current flow into the brain and of the depth of current density (Miranda et al., 2006). Fig. 1 illustrates these principles and shows four standard stimulation sites of tDCS in neuropsychology for different sensory, motor or cognitive research questions.

In a study using a computer-based model Wagner et al. (2007) found that the strength of the current density in the cortex depends on the following factors: size, polarity and position of the electrodes, the applied current intensity and the properties of the tissue in the stimulated area. Approximately 45% of the current delivered to the skull reaches the surface of the cortex (Rush & Driscoll, 1968). Once the electrodes are placed the current intensity has to be raised in a ramp-like fashion until the desired level is reached. During the flow of the current subjects usually feel a mild tingling sensation which disappears after a few seconds when current intensity is below 1.5 mA (Hummel & Cohen, 2005). For *subliminal* stimulation the individual sensory threshold has to be determined as follows. The current intensity is increased in small steps of 0.1 mA until the subject perceives a mild tingling beneath the electrodes. Then the current is decreased by 0.3 mA and gradually increased again until the tingling recurs. This procedure yields an estimate of the current intensity which induces a just perceptible tingling. The sensory threshold is set at 90% of this value (Wilkinson, Ko, Kilduff, McGlinchey, & Milberg, 2005).

For *sham* stimulation the electrodes are placed in the same way as for real (verum) stimulation and the current intensity is increased in both conditions in a ramp-like fashion. However, in the case of sham stimulation the current is gradually turned off after a few seconds. Subjects are not able to distinguish between verum and placebo stimulation, which makes the method an attractive research tool in the field of neurorehabilitation and cognitive neuroscience. It is more difficult to achieve a convincing sham condition for other stimulation methods. For example in the case of TMS a specific pattern of noise, constant tap sensation and in some cases muscle twitches are produced. Sham stimulation typically involves discharging a TMS coil which is not held to the skull. This reproduces the noise, but not the tap sensation or muscle twitches (Gandiga, Hummel, & Cohen, 2006). In contrast, subsensory or sham-stimulation in neuroscientific research with tDCS is convincing and easy to realize.

In summary, the application of tDCS is easy to handle. However there are limitations both in its low focality, because of the large electrode sizes (Nitsche et al., 2007), and its low temporal resolution (Schlaug, Renga, & Nair, 2008).

2.4. Safety

Concerning the safety of tDCS, a stimulation intensity of up to 2 mA and a duration of about 20 min is considered to be safe (Iyer et al., 2005; Nitsche, Liebetanz, et al., 2003). The observed adverse effects are minor and consist of light itching beneath the electrodes or mild headache during sham and verum stimulation (Fregni, Boggio, Lima, et al., 2006). Such effects have been observed for different cortical areas in healthy subjects as well as in patients with different neurological disorders (Poreisz, Boros, Antal, & Paulus, 2007).

Repeated sessions of tDCS did not result in different frequencies of adverse effects (headache, itching) in groups receiving verum stimulation compared with placebo stimulation groups. In addition, there were no adverse cognitive effects in these studies as indicated by a neuropsychological test battery. This battery included tests of global cognitive functions, attention and working memory capacity, processing speed, focused and sustained attention and design fluency (Fregni, Boggio, Lima, et al., 2006; Fregni, Boggio, Nitsche, Rigonatti, & Pascual-Leone, 2006; Fregni, Gimenes, et al., 2006).

During MRI no changes of the blood-brain barrier or cerebral tissue appeared while stimulating the frontal cortex (Nitsche, Niehaus, et al., 2004). Furthermore, 13 min of tDCS did not result in alterations of the serumneuron-specific enolase concentration (Nitsche & Paulus, 2001), which is a sensitive indicator of neuronal damage.

Although not directly transferable to humans, a recent animal study by Liebetanz et al. (2009) determined the safety limits of cathodal tDCS. Rats received cathodal stimulation *via* an epicranial electrode and brain tissue damage was assessed. More than 10 min stimulation with a current density of 142.9 A/m^2 resulted in brain lesion. Lesion size rose linearly with charge density for current densities between 142.9 and 285.7 A/m^2 and was zero if a charge density was below 52400 Coloumb/m^2. Hence, brain damage will result if threshold for current and the charge density are exceeded. The charge density of 171–480 Coloumb/m^2 that is currently used in human participants falls far below this quantified threshold and suggests that stimulation protocols of increased intensity would remain within safe limits but this would need to be confirmed by further animal research.

Human subjects who had undergone recent brain neurosurgery or who have metallic implants within their brain should be

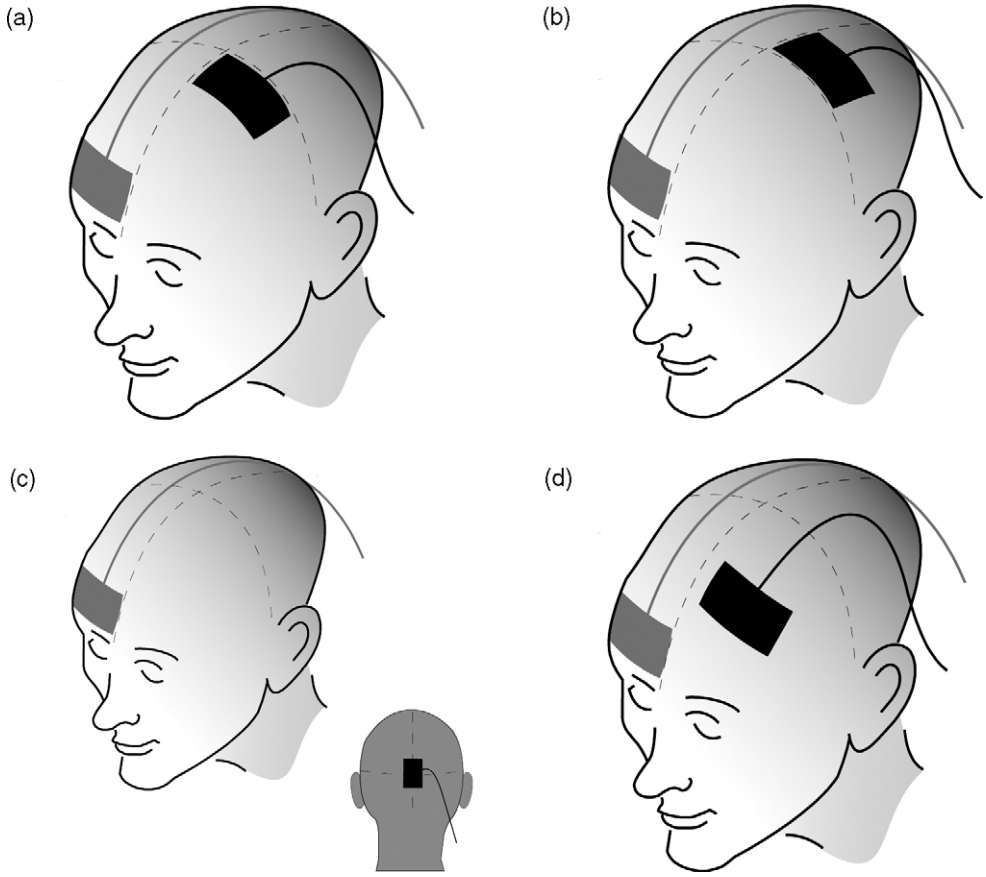

Fig. 1. Demonstration of 4 typical electrode locations on the skull surface when using tDCS. The four figures illustrate the typical placement of anode and cathode during stimulation of the primary motor cortex (A), somatosensory cortex (B), primary visual cortex (C), anterior language cortex (D). Note that in Fig. 1(C) one electrode is placed at the back of the head (see small image of the head), while the other electrode is placed at the right supra-orbital area. One electrode is placed on the area of the skull covering the target structure and the other electrode is typically placed either over the supraorbital area of the other hemisphere or over the corresponding area of the contralateral hemisphere. Note, that other stimulation positions have been used as well (see text for details).

excluded from stimulation for safety reasons. Further exclusion criteria are a sensitive skin on the scalp and signs of epilepsy. Furthermore it should be noted that certain medications modulate the effects of tDCS, such as neuroleptic and antiepileptic drugs, antidepressants, benzodiazepines and L-Dopa (Hesse et al., 2007). When these safety criteria are adhered to, approximately 80% of neurological patients with chronic cerebrovascular disorders (i.e. stroke, intracerebral bleeding) are eligible for tDCS studies according to our experience. In order to monitor possible adverse effects of tDCS a questionnaire (Poreisz et al., 2007) or visual analog scales (Gandiga et al., 2006), containing questions about headache, mood changes, attention, fatigue or discomfort are recommended.

In sum tDCS is a safe stimulation method when certain standard procedures are followed. Nonetheless, further safety studies concerning longer stimulation intervals and higher stimulation intensities are necessary, especially when brain-lesioned subjects are to receive repetitive tDCS or single-session tDCS with higher current intensities (>1.5 mA), or when repeated applications are performed for therapeutic purposes.

2.5. Physiological mechanisms of action

The mechanisms of action of tDCS have yet to be elucidated. It has been frequently found that anodal (surface-positive) stimulation increases the spontaneous firing rate and the excitability of cortical neurons by depolarizing the membranes, whereas cathodal (surface-negative) stimulation leads to hyperpolarization of the neurons membranes and thus invokes a decrease of the neuronal firing rate and excitability (see Fig. 2). This pattern of activity was first shown in animals receiving stimulation *via* epidural or intracerebral electrodes (Bindman, Lippold, & Redfearn, 1962; Creutzfeldt, Fromm, & Kapp, 1962; Purpura & McMurtry, 1965). The direction of cortical modulation is however not solely polarity-dependent, but also determined by the type and the spatial orientation of neurons as well as the stimulation intensity: Creutzfeldt et al. (1962) demonstrated that neurons in deeper layers of the cat motor cortex are activated by cathodal and inhibited by anodal stimulation,

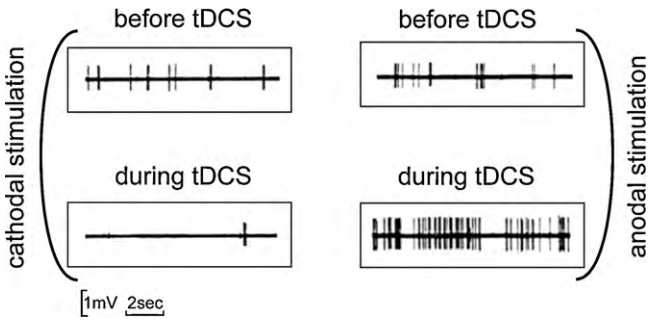

Fig. 2. Illustration of the physiological mechanisms of anodal (right side of figure) and cathodal (left side of figure) transcranial direct current stimulation on spike activity in animals (adapted and modified after Bindman et al., 1964). Anodal stimulation increased subsequent spike activity by lowering the membrane potential whereas cathodal stimulation reduced subsequent spike activity in the stimulated area by increasing the membrane potential.

probably as a result of the inversion of current flow associated with the neuron's spatial orientation. Furthermore, high current intensities are required to activate pyramidal cells, whereas non-pyramidal neurons are activated by weak stimulation strength (Purpura & McMurtry, 1965). Sustained excitability elevations have also been demonstrated in these early animal studies. Bindman et al. (1962) and Bindman, Lippold, and Redfearn (1964) showed aftereffects lasting for hours, induced by anodal cortical stimulation of 5–10 min in the rat (Bindman et al., 1962, 1964) which seem to be protein synthesis-dependent (Gartside, 1968).

Effects of tDCS in humans are quite consistent with the physiological mechanisms found in animals. Anodal stimulation increases cortical excitability, whereas cathodal stimulation has the reverse effect (Nitsche & Paulus, 2000). Nitsche and Paulus (2001) demonstrated prolonged aftereffects of tDCS up to 90 min in human motor cortex. The duration of these effects depend on stimulation duration and current intensity.

Pharmacological studies have shown that voltage-dependent ion channel blockers like carbamazepine and flunarizine diminish or even eliminate the effects during tDCS as well as the aftereffects of anodal stimulation (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche, Fricke, et al., 2003). On the other hand, the NMDA-receptor-antagonist dextromethorphane impedes the long-term effects of tDCS, irrespective of polarity (Nitsche, Fricke, et al., 2003). The authors conclude, that polarization effects of the neuronal membrane are responsible for the short-term effects of tDCS, whereas the long-lasting effects are caused by the modulation of NMDA receptor strength. Further evidence concerning the importance of NMDA receptors for the generation of aftereffects of tDCS comes from the observation that the partial NMDA agonist D-Cycloserine prolongs anodal tDCS-induced excitability enhancements (Nitsche, Jaussi, et al., 2004). The same is true for amphetamine, a catecholaminergic re-uptake-blocker, whose effects are prevented by additional application of an NMDA receptor antagonist (Nitsche, Grundey, et al., 2004). The shortening of anodal tDCS-induced aftereffects by application of the β-adrenergic antagonist proanolol indicates that the consolidation of the NMDA receptor-modulated cortical excitability modifications depends on adrenergic receptors (Nitsche, Grundey, et al., 2004). Cathodal tDCS-generated excitability reductions for up to 24 h after the end of stimulation were induced by dopaminergic receptor (D2) activation (Nitsche et al., 2006).

On the basis of these observations Liebetanz et al. (2002) and Nitsche, Fricke, et al. (2003) suggested NMDA receptor-dependent long-term potentiation (LTP) and long-term depression (LTD) as possible candidates for the explanation of the tDCS aftereffects. Both LTP and LTD are well-known phenomena of neuroplasticity. In contrast, Ardolino, Bossi, Barbieri, and Priori (2005) postulate a non-synaptic mechanism underlying the long-term effects of cathodal tDCS. They suggest that these long-term effects are caused by alterations in neuronal membrane function, possibly arising from changes in pH and in transmembrane proteins.

Nitsche et al. (2005) examined the excitability modulation generated by tDCS of the motor cortex *via* alterations of TMS parameters by tDCS. Global measures of cortico-spinal excitability such as motor thresholds and input–output curves were assessed as well as indirect wave (I-wave) interactions, intracortical facilitation and inhibition. I-waves are cortico-spinal waves, emerging after the first cortico-spinal burst and are presumably controlled by intracortical neuronal circuits. Nitsche et al. (2005) conclude that short-term stimulation depends on the alteration of subthreshold resting membrane potentials. In contrast, aftereffects are induced by changes of intracortical facilitation and inhibition.

3. Procedure for GVS

3.1. History

The history of GVS is like the history of tDCS based on Galvani's (1791) and Volta's (1792) experiments on animal and human electricity (see Section 2.1). Volta was the first who reported on the perceptual effects of electric stimulation in 1790, when putting electrodes in his ears. He felt a twitch and spinning in his head and heard a noise, which is unsurprising with a current strength of approximately 30 V. Breuer and Hitzig reported illusory body movement during stimulation with the electrodes placed on the mastoids.

In 1820 Johann Purkyne systematically investigated the dizziness and disturbance of balance induced by galvanic stimulation. The first report on nystagmus resulting from galvanic stimulation stems from Hitzig who experimented on dogs and humans. By the combination of labyrinthectomy and galvanic stimulation in animals, Josef Breuer showed the vestibular origin of the induced nystagmus and balance distortions. Since that time GVS has been used for the investigation of the vestibular system in animals and humans (for a review see Fitzpatrick & Day, 2004).

3.2. Method

Stimulation of the vestibular system can be induced when the anode and cathode are applied to the left and right mastoids (or *vice versa*) behind the ears. This form of direct current stimulation is termed Galvanic Vestibular Stimulation (GVS). Underneath the mastoids the vestibular nerve runs from the inner ear towards vestibular brain stem nuclei, which in turn are interconnected with thalamic relay stations (nucleus ventroposterolateralis). From there, ascending vestibular fiber pathways reach a number of cortical vestibular areas including area 2cv near the central sulcus, area 3a,b in the somatosensory cortex, parietal area 7a, and the parieto-insular-vestibular-cortex (PIVC; Guldin & Grusser, 1998). Although there is no primary vestibular cortex as in the visual, auditory or tactile modality, the above-mentioned array of multiple, interconnected vestibular cortical areas is thought to be under the control of the PIVC. Fig. 3 illustrates schematically the mechanisms of GVS *via* stimulation of the mastoids behind the ears as well as the main anatomical pathways including subcortical and cortical relay stations.

3.3. Positioning of the electrodes

Stimulation with two electrodes of different polarity placed behind the mastoids is more precisely termed *bilateral bipolar GVS*. There are other electrode montages such as unilateral monopolar GVS, at which only one electrode is placed behind one ear or bilateral monopolar stimulation with two electrodes of the same polarity on both mastoids and a remote electrode of the other polarity (Fitzpatrick & Day, 2004). The application of the electrodes is identical to that of tDCS to the skull, as are most of the other features. Note however, that the physiological mechanism of action is different in GVS as tDCS as the current runs from the periphery to the cortex in GVS, whereas it runs directly from the skull into the underlying cortex in tDCS. Like tDCS, GVS is well suited for subliminal stimulation so that the subject is unaware of verum or placebo (sham) stimulation. This is an important advantage in neuroscientific research as the placebo or sham stimulation conditions can be more efficiently realized than with TMS.

3.4. Physiological mechanisms of action

GVS acts on the entire vestibular nerve *via* polarization effects, hence on otoliths *and* the semicircular canal, but not on the vestibular end organ (Stephan et al., 2005). This activation pattern is different from other vestibular stimulation techniques, for instance caloric vestibular stimulation which activates only the horizontal semicircular canal (Bottini et al., 1994; Dieterich et al., 2003), which in turn causes nystagmus.

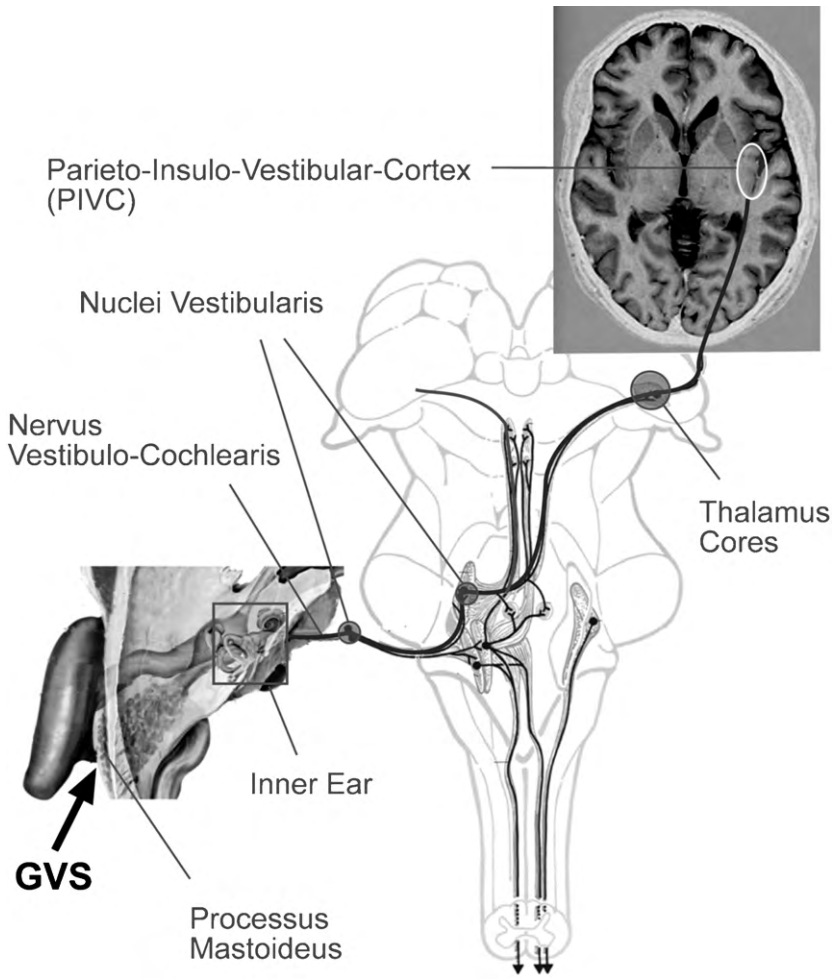

Fig. 3. Schematic illustration of the mechanisms of Galvanic Vestibular Stimulation (GVS). Stimulation at the mastoids (see arrow) activates the vestibular nerve, and subsequently all vestibular relay stations located upstream including nervus vestibulo-cochlearis, vestibular nuclei in the brainstem, thalamic nuclei and finally the parieto-insular vestibular cortex (PIVC), as well as adjacent areas such as the temporoparietal junction and the parietal cortex (not indicated).

Functional imaging studies of GVS using direct current stimulation (Bense, Stephan, Yousry, Brandt, & Dieterich, 2001; Bucher et al., 1998) have revealed a network of activated multisensory cortical areas including the insular and retroinsular regions, the superior temporal gyrus, temporo-parietal cortex, the basal ganglia and the anterior cingulate gyrus. Moreover, Fink et al. (2003) showed activations of the PIVC and the temporoparietal junction area during GVS in healthy subjects. Notably, left-anodal/right-cathodal GVS led to a *unilateral* activation of the right-hemispheric vestibular system, while left-cathodal/right-anodal GVS led to a *bilateral* activation of both vestibular cortices.

3.5. Safety

Until now, no formalized safety studies of GVS have been published to our knowledge. However, from our own experience with more than 50 patients with right-hemispheric stroke and 20 healthy subjects we know that subliminal (below the sensory threshold) GVS with approximately 0.6–0.8 mA current intensity for a maximum of 20 min is safe and does not produce any adverse effects in any of these 70 subjects (Utz, Kerkhoff, Oppenländer, unpublished observations).

In the following sections we will review studies that have used either tDCS or GVS in different fields of neuropsychology.

4. tDCS of the motor cortex

Most of the pioneering studies investigating the effects of tDCS on the modulation of cortical function were done on motor cortex (Nitsche & Paulus, 2000). The anatomy and physiology of motor cortex is comparatively well understood and previous TMS work on motor cortex has provided further information about how cortical stimulation affects the response of the motor system. This offers the opportunity to use motor-response parameters to quantify the effects of cortical stimulation. Two main groups of tDCS studies on motor cortex can be distinguished: (1) studies which use the motor cortex to investigate the physiological mechanisms underlying tDCS and (2) studies which use tDCS to study the function of the motor cortex and how its modulation affects motor behaviour. This section chiefly considers the second group (see Table 1 for a summary of the reviewed studies).

In a study with 24 healthy subjects (Cogiamanian et al., 2007) the effect of anodal stimulation of the right motor cortex on neuromuscular fatigue was investigated. Neuromuscular fatigue is the exercise-dependent decrease in muscle force which results from peripheral and cortical factors. This is relevant for many motor functions in daily life (Cogiamanian et al., 2007). Ten minutes of anodal tDCS (1.5 mA current intensity, motor cortex stimulation) produced a significant (15%) reduction in fatigue while cathodal tDCS and sham tDCS at the same site were ineffective. Hence, anodal tDCS may increase muscle endurance – a finding which may be of

Table 1
Selection of studies using tDCS of the motor cortex.

Reference	Type of study	Position of electrodes	Stimulation parameters	Population	Effects
Boggio, Castro, et al. (2006)	Sham-controlled modulation study	One electrode over the right/left M1 at C3/C4[a] and the other electrode over the contralateral supraorbital area	1 mA for 20 min, 2 sessions, anodal vs. sham	8 healthy subjects	Enhancement of motor performance of the non-dominant hand after anodal stimulation of right M1
Boggio et al. (2007)	Sham-controlled-treatment study	M1 at C3/C4[a] (for anodal stimulation: anode over the M1 of the affected hemisphere; for cathodal stimulation: cathode over the M1 of the unaffected hemisphere); the other electrode over the contralateral supraorbital area	1 mA for 20 min/day, 4 sessions, anodal vs. cathodal vs. sham; 1 mA for 20 min/day, 5 sessions cathodal tDCS	9 stroke patients	Improvement of hand motor functions after anodal stimulation of M1 of the affected hemisphere and as well after cathodal stimulation of the unaffected hemisphere; similar improvement magnitude from both stimulation conditions; lasting effects after 5 sessions of cathodal tDCS of the unaffected hemisphere at 2-week-follow-up
Boros et al. (2008)	Modulation study	One electrode over the left premotor cortex (2.5 cm anterior to the left M1), the left DLPFC at F3[a] and the other electrode above the contralateral orbita	For anodal stimulation: 1 mA for 13 min, for cathodal stimulation: 1 mA for 9 min, 2 sessions anodal vs. cathodal	17 healthy subjects	Increased excitability of the ipsilateral motor cortex after anodal stimulation of the left premotor cortex in comparison to cathodal tDCS and anodal tDCS of the DLPFC; duration of effects: 30 min
Cogiamanian et al. (2007)	Modulation study	One electrode over the right motor cortex and the other electrode above the right shoulder	1.5 mA for 10 min, 2 sessions, anodal vs. cathodal	24 healthy subjects	Amelioration of neuromuscular fatigue after anodal stimulation of the right motor cortex; increase in endurance time of elbow flexor muscles in a submaximal isometric task 1 h after baseline fatigue task
Fregni, Boggio, Mansur, et al. (2005)	Double-blind, sham-controlled modulation study	M1 at C3/C4 (for anodal stimulation: anode over the M1 of the affected hemisphere; for cathodal stimulation: cathode over the M1 of the unaffected hemisphere); the other electrode over the contralateral supraorbital area	1 mA for 20 min, 3 sessions, anodal vs. cathodal vs. sham	6 stroke patients	Improvement of hand motor functions after anodal stimulation of M1 of the affected hemisphere and as well during and immediately after cathodal stimulation of the unaffected hemisphere
Hummel et al. (2006)	Pseudo-randomized, double-blind, sham-controlled, cross-over modulation study	Anode over M1 of the affected hemisphere and the cathode over the contralateral supraorbital area	1 mA for 20 min, anodal vs. sham	11 stroke patients	Improvement of hand motor functions measured as pinch force and reaction times of the paretic hand after anodal stimulation of the affected hemisphere
Jeffery et al. (2007)	Sham-controlled modulation study	One electrode over the left M1 (leg area) and the other electrode above the contralateral orbita	2 mA for 10 min, 3 sessions, anodal vs. cathodal vs. sham	8 healthy subjects	Increase in the excitability of the leg corticospinal tract after anodal stimulation; duration of effects: 60 min

Table 1 (*Continued*)

Reference	Type of study	Position of electrodes	Stimulation parameters	Population	Effects
Lang et al. (2004)	Modulation study	One electrode over the left M1 and the other electrode over the contralateral orbita	1 mA for 10 min, 2 sessions, anodal vs. cathodal	8 healthy subjects	Increase after anodal and decrease after cathodal stimulation of the left M1 in MEPs evoked from the same hemisphere; duration of effects: <40 min; no changes in MEPs from right M1; effect on transcallosal inhibition only from right M1 (prolonged effect after anodal and shortened after cathodal tDCS)
Lang et al. (2005)	Sham-controlled modulation study; (PET)	One electrode over the left M1 and the other over the contralateral frontopolar cortex	1 mA for 10 min, 2 sessions, anodal vs. cathodal vs. sham	10 healthy subjects	Widespread increase and decrease in regional cerebral blood flow in cortical and subcortical areas of both hemispheres by anodal as well as cathodal stimulation; increase of rCBF after real tDCS (irrespective of polarity) in left M1, right frontal pole, right sensorimotor cortex, posterior brain regions; duration of effects: 50 min (during the PET scan).
Power et al. (2006)	Sham-controlled modulation study	One electrode over the left motor cortex and the other electrode over the contralateral orbita	1 mA for 10 min, 3 sessions, anodal vs. cathodal vs. sham	10 healthy subjects	Increase in MEP size and in β-band intermuscular coherence after anodal stimulation; decrease in the same parameter after cathodal stimulation; duration of effects: 5–10 min, partially significant
Quartarone et al. (2004)	Sham-controlled modulation study	One electrode over the left M1 (motor cortical representation field of the right first dorsal interosseous muscle)[b] and the other electrode above the contralateral orbita	1 mA for 5 min, 3 sessions, anodal vs. cathodal	21 healthy subjects	Effects on cortical excitability (reduction of MEP size) during motor imagery by cathodal stimulation; duration of effects: 30 min; no effects after anodal stimulation
Reis et al. (2009)	Sham-controlled treatment study	Left M1 and above the contralateral supraorbital area	1 mA for 20 min, 5 sessions anodal vs. cathodal vs. sham	36 healthy subjects	Facilitation of motor learning after repetitive anodal stimulation; duration of effects: 3 months

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; left/right: stimulation was conducted over the same cortical area in the left and the right hemisphere separately; MEP: motor evoked potentials.

[a] According to the international 10/20 EEG System.

[b] Revealed by TMS.

relevance to sports science but also of potential clinical interest for patients with pathologically altered muscle endurance. The data are in line with recent data showing that anodal tDCS of the motor cortex improves hand function in healthy subjects or patients with stroke (see below).

Lang, Nitsche, Paulus, Rothwell, and Lemon (2004) tested the influences of 10 min of anodal or cathodal tDCS applied to the left primary motor cortex (M1) on the following two parameters: (1) corticospinal excitability of the left and right motor cortex as measured by motor evoked potentials, and (2) transcallosal excitability between the motor cortices as measured by the onset latency and duration of transcallosal inhibition, in both cases assessed by TMS. Anodal tDCS over the left primary motor hand area (M1) increased the MEPs (+32%), whereas cathodal stimulation of the same location decreased MEPs (−27%). The duration of the aftereffect (40 min post-test) was longer in the cathodal condition. MEPs evoked from the right M1 were not affected, but the duration of inhibition from M1 was reduced after cathodal tDCS, and prolonged after anodal tDCS (Lang et al., 2004). The results indicate that the effects of tDCS were restricted to the hemisphere that was stimulated (but see the different results of the PET study by Lang et al., 2005). Power et al. (2006) also showed modulating effects of tDCS on motor evoked potentials. In this study, increased MEPs after anodal tDCS were accompanied by increased intramuscular coherence, and a decrease after cathodal tCDS. Sham stimulation influenced none of the parameters. Furthermore, tDCS seemed to also affect deeper seated parts of the motor cortex such as the leg area. Anodal tDCS of 2 mA intensity for 10 min increased the excitability of corticospinal tract projection to the tibialis anterior muscle of the lower leg as assessed by TMS-evoked MEPs (Jeffery, Norton, Roy, & Gorassini, 2007). On the contrary, cathodal tDCS under the same stimulation conditions seemed to produce only small changes in MEPs assessed at rest or during contraction of the tibialis anterior muscle.

A recent study by Boros, Poreisz, Munchau, Paulus, and Nitsche (2008) provided evidence that tDCS activates not only the directly stimulated area (the area under the location of the current application) but also interconnected brain areas within the same hemisphere. Anodal tDCS of the premotor cortex increased the excitability of the ipsilateral motor cortex compared with cathodal tDCS of the premotor cortex and anodal tDCS of the dorsolateral prefrontal cortex (DLPFC). These results may be taken as an indication that cortical activity can be modulated indirectly *via* tDCS of remote but interconnected brain areas. This indirect brain stimulation technique may be useful in certain pathological conditions, such as pain (see Section 8.2).

In a PET study (Lang et al., 2005) the aftereffects of 10 min of anodal and cathodal tDCS over the left M1 on regional cerebral blood flow were investigated. When compared with sham tDCS, anodal and cathodal tCDS induced widespread increases and decreases in regional cerebral blood flow in cortical *and* subcortical areas of *both* cerebral hemispheres. Interestingly, these changes in regional cerebral blood flow were of the same magnitude as task-related changes observed during finger movements. Both real tDCS conditions induced increased blood-flow in the left motor hand cortex, the right frontal pole, right primary sensorimotor cortex and posterior brain regions. Apart from some exceptions, anodal stimulation resulted in a widespread activation of dorsal brain areas (post-central sulcus, premotor cortex, SMA, prefrontal cortex, parietal cortex, precuneus, superior temporal gyrus, superior occipital sulcus) whereas cathodal stimulation mainly activated more ventral cortical areas (superior temporal sulcus and gyrus, insula, posterior cingulate gyrus, inferior occipital lobe). The effects were sustained for the duration of the PET scanning period (50 min). In sum, this important study shows long-lasting and widespread effects of 10 min tDCS on cortical blood flow. Although the complex activation patterns observed may in part depend on the precise location of the electrodes, it is obvious that tDCS not only induces activations or deactivations close to the electrodes, but also remote effects in *both* cerebral hemispheres, the latter indicating transcallosal interactions.

Boggio, Castro, et al. (2006) showed that anodal tDCS (20 min, 1 mA) compared with sham stimulation of the non-dominant M1 improved motor function as assessed by the Jebson Taylor Hand Function Test. This was not found for anodal and sham stimulation of the dominant M1. The authors assume that these results reflect cortical plasticity associated with the under-used non-dominant hand (Boggio, Castro, et al., 2006). Quartarone et al. (2004) investigated motor imagery, namely the effects of tDCS on imagined movements of one's own index finger. Subjects were required to imagine the abduction of their right index finger. Muscular relaxation in the course of the task was controlled by audio-visual EMG monitoring. Only cathodal tDCS over the left M1 reduced the size of the MEP amplitudes by 50% in the mental motor imagery paradigm while anodal tDCS had no effect. The aftereffects of cathodal tDCS lasted for up to 30 min.

DC stimulation also influences *long-term* skill motor learning. Reis et al. (2009) used a computerized motor skill task to evaluate the effects of anodal tDCS on the course of learning. They measured speed and accuracy in this task as online effects (within one training day), offline effects (between training days), short-term training effects (within 5 days of motor training) and long-term effects (at 3-month follow-up). The experimental training group received 5 sessions of 20 min anodal tDCS (1 mA, left M1 stimulation) whereas the two control groups received either sham stimulation or cathodal tDCS under the same study conditions. Anodal tDCS showed greater effects on the total learning effect (online + offline effects for the whole training period of 5 days) as cathodal or sham stimulation. These beneficial effects were maintained at follow-up, when the anodal group still performed better than the two other groups (Reis et al., 2009). These results demonstrate a facilitation of motor learning induced by multi-session, anodal tDCS of the motor cortex.

Another research field that has been opened by tDCS research is the induction of neuroplastic changes in stroke patients with contralateral hemiparesis. Fregni, Boggio, Mansur, et al. (2005), addressed the issues of stimulation condition (anodal vs. cathodal) and hemisphere (lesioned vs. intact) in 6 chronic (lesion age: 27 months), hemiparetic stroke patients. The patients received, in a counterbalanced design, either anodal tDCS over M1 of the affected hemisphere, or cathodal tDCS over M1 of the unaffected hemisphere or sham tDCS. The two verum stimulations (1 mA for 20 min, the other electrode at supraorbital area) showed significant improvements in the Jebsen-Taylor hand function test as assessed *after* tDCS. In contrast, only the cathodal tDCS over M1 of the unaffected hemisphere produced an *online* effect during stimulation, although the difference to the effect obtained with anodal tDCS was not statistically significant. A recent study by Boggio et al. (2007) replicated these findings in a new patient sample. Hummel et al. (2006) investigated the impact of anodal, cathodal and sham tDCS (1 mA for 20 min. over M1 of the motor cortex) of the affected hemisphere on performance in daily motor activities as assessed by the Jebsen-Taylor hand function test. All 6 patients showed contralateral hand pareses after ischemic brain infarctions sparing the primary motor cortex. Remarkably, every patient benefited from anodal tDCS but not sham or cathodal tDCS. These benefits outlasted the stimulation and correlated with parameters of motor cortical excitability as measured by TMS. Brain stimulation *via* tDCS may have an important adjuvant role in the treatment of motor impairments after stroke (see also Section 9.1).

To summarize, the studies reported here reveal that tDCS changes cortical excitability in the motor system and improves performance in daily motor tasks as well as motor learning and motor cognition, both in healthy subjects and clinical populations. Whilst

the first clinical studies show very promising results of tDCS in motor rehabilitation they need to be replicated in larger, randomized controlled patient studies.

5. tDCS of the visual cortex

A number of studies have addressed the effects of tDCS on vision both in behavioural and electrophysiological paradigms (summarized in Table 2). Antal, Nitsche, and Paulus (2001) showed a reduction in contrast sensitivity during cathodal stimulation, but no improvement with anodal visual cortex stimulation. Cathodal tDCS of area V5 impaired visual motion discrimination while anodal stimulation improved it (Antal, Nitsche, et al., 2004). Other studies measured visual evoked potentials to study the effects of tDCS on visual-cortex activity. When stimulating over the occipital cortex (presumably V1) for at least 10 min, and using low-contrast stimuli, an increase in the N70 component was found with anodal stimulation and a decrease of this component with cathodal stimulation (Antal, Kincses, Nitsche, Bartfai, & Paulus, 2004). Significant aftereffects were also shown in this study. In a related study, Accornero, Li Voti, La Riccia, and Gregori (2007) found slightly different results: they reported a decreased P100 component with anodal occipital stimulation and an increased P100 amplitude with cathodal stimulation. The differences are probably related to differences in the placement of the second electrode in the two studies. Finally, Antal, Varga, Kincses, Nitsche, and Paulus (2004) showed a decrease of the normalized gamma-band frequencies with cathodal occipital stimulation and a slight increase with anodal stimulation of the same site. This finding indicates that occipital DCS can alter neural networks involved in higher order cognitive functions (Herrmann, Munk, & Engel, 2004).

In clinical populations, tDCS over the visual cortex might be a promising technique to modulate residual visual capacities (Ro & Rafal, 2006), investigate blindsight (Stoerig & Cowey, 1997), or enhance treatments for patients with postchiasmatic visual field defects, for whom currently a number of successful *compensatory* treatment techniques have been developed (i.e. scanning: Roth et al., 2009; reading: Spitzyna et al., 2007; for a review see: Lane, Smith, & Schenk, 2008). However, no effective treatment for the visual field loss itself is currently available (Glisson, 2006). The upgrading of dysfunctional, perilesional remnants of the visual cortex or unmasking of subcortical visual areas important for visuomotor capacities might be achieved by anodal, occipital tDCS and assist compensatory treatment methods or even lead to novel visual treatments (Kerkhoff, 2000; Ro & Rafal, 2006).

In sum, until now, few studies have addressed the potential effects of tDCS of the visual cortex, especially of cortical visual areas beyond V1. The available evidence – mostly derived from stimulation of the primary visual cortex (V1, Oz electrode location) in healthy subjects – suggests modulatory effects in visual sensitivity or motion discrimination (after V5-stimulation) as well as significant aftereffects following 10–20 min of stimulation. In light of the known cortical architecture of the visual system and its multiple pathways and processing stages from V1 to more than 32 cortical and subcortical visual areas (Felleman & Van Essen, 1991) many interesting hypotheses remain to be tested: Does tDCS of the right occipito-temporal cortex modulate face perception or categorization, or that of the left occipito-temporal cortex shape or object perception and categorization (or *vice versa*)? What effects are obtained with tDCS of the superior temporal sulcus on the perception of social cues from the face (analogous to the effects of electrical stimulation with intracranial electrodes, cf. Allison, Puce, & McCarthy, 2000)? Can tDCS of the left or right lingual gyrus influence colour perception, categorization or colour imagery? Technically, it is easier to reach such ventral brain structures *via* tDCS than with TMS without inducing often painful activation of nearby nerves. Finally, future studies could investigate the effect of tDCS over different dorsal visual stream areas, such as the left or right parieto-occipital cortex to test its influence on visuospatial cognition, such as the judgment of spatial positions, orientation discrimination and the subjective visual vertical or constructional apraxia.

6. tDCS of the parietal cortex

6.1. Somatosensory cortex

Rogalewski, Breitenstein, Nitsche, Paulus, and Knecht (2004) tested the influence of stimulation of the somatosensory cortex on tactile discrimination of vibratory stimuli delivered to the left ring finger. They found that 7 min of cathodal but not anodal or sham stimulation disrupts tactile perception. Likewise, Dieckhofer et al. (2006) showed that cathodal stimulation decreased low-frequency components of somatosensory evoked potentials (SEPs) after contralateral median nerve stimulation. In another study, Ragert, Vandermeeren, Camus, and Cohen (2008) established that 20 min of anodal tDCS over the primary somatosensory cortex improves spatial tactile acuity in the contralateral index-finger. Furthermore, anodal tDCS of the primary somatosensory cortex led to long-lasting increases of SEPs recorded from the contralateral median nerve at the wrist. In contrast, no effects on SEPs were obtained after stimulation of the left median nerve or cathodal tDCS (Matsunaga, Nitsche, Tsuji, & Rothwell, 2004). Differences in stimulation duration and in size (Ragert et al., 2008) or location of the electrodes could have led to the diverging results (Dieckhofer et al., 2006).

In clinical populations (i.e. stroke, hemorrhage) somatosensory disturbances are a frequent (>50%, cf. Groh-Bordin & Kerkhoff, 2009) and disturbing occurrence which not only impaires touch and tactile object recognition but also motor performance. tDCS of the somatosensory cortex might be a promising add-on-technique that could augment the effects of behavioural trainings known to improve somatosensory capacities (Groh-Bordin & Kerkhoff, 2009; Wang, Merzenich, Sameshima, & Jenkins, 1995; Yekutiel & Guttman, 1993). Table 3 summarizes the reviewed studies concerning tDCS of the parietal cortex.

6.2. Posterior parietal cortex

So far, only a few studies have investigated the effects of tDCS of the posterior parietal cortex. Stone and Tesche (2009) investigated the effects of anodal and cathodal stimulation of the left posterior parietal cortex (P3 electrode location according to the 10–20 EEG reference system) on attentional shifts from global to local features and *vice versa* in 14 healthy subjects using single vs. compound letter stimuli. Their results indicate that cathodal stimulation acutely degraded attentional switches during stimulation, and anodal stimulation persistently degraded local-to-global attentional switching for at least 20 min after stimulation. These results support the involvement of the left parietal cortex in attentional switching. Another recent study by Sparing et al. (2009) addressed the question of interhemispheric parietal (im)balance in 20 healthy subjects and 10 patients with left spatial neglect using anodal and cathodal parietal stimulation (P3 and P4 electrode location). Sparing et al. (2009) found in their healthy subjects, that anodal stimulation enhanced visual target detection in the contralateral visual field in a demanding detection task, whereas cathodal stimulation depressed detection performance in the same task in the contralateral hemifield. Furthermore, the effects of anodal and cathodal tDCS were complementary: left parietal anodal stimulation had similar effects on target detection in the right visual field as right parietal cathodal stimulation and *vice versa*.

Table 2
Selection of studies using tDCS of the visual cortex in healthy subjects.

Reference	Type of study	Position of electrodes	Stimulation parameters	Population	Effects
Accornero et al. (2007)	Modulation study	One electrode at Oz[a], the other electrode at the base of the posterior neck	1 mA for 3–10 min	20 healthy subjects	Increase of P100 amplitude during anodal stimulation and decrease during cathodal stimulation
Antal et al. (2001)	Modulation study	One electrode at Oz[a], the other electrode at Cz[a]	1 mA for 9 min, 2 sessions, anodal vs. cathodal	15 healthy subjects	No effect of anodal stimulation on static and dynamic contrast sensitivity. Cathodal stimulation impaired both dynamic and static contrast sensitivity during and up to 10 min post-stimulation
Antal, Nitsche, et al. (2004)	Modulation study	One electrode at left V5, the other at Cz[a]	1 mA for 10 min, 2 sessions, anodal vs. cathodal	8 healthy subjects	Modified motion perception threshold during anodal and cathodal stimulation
Antal, Kincses, et al. (2004)	Modulation study	One electrode at Oz[a], the other at Cz[a]	1 mA for 20 min, 2 sessions, anodal vs. cathodal	20 healthy subjects	Increase in the N70 amplitude of the visual evoked potential during and up to 10 min after anodal stimulation. Cathodal stimulation without effect
Antal, Varga, et al. (2004)	Modulation study	One electrode at Oz[a], the other at Cz	1 mA for 10 min, 2 sessions, anodal vs. cathodal	12 healthy subjects	Cathodal stimulation decreased normalized gamma and beta oscillatory frequencies in the evoked potential while anodal stimulation slightly increased it

[a] According to the international 10/20 EEG System.

Hence, the activation of the left parietal cortex and the deactivation of the right parietal cortex resulted in a similar performance increase in the right hemifield. Moreover, Sparing et al. (2009) found that *deactivating* the left (anatomically intact) parietal cortex with cathodal tDCS in patients with left visual hemineglect after right-hemisphere stroke led to an improvement in leftsided visual target detection, while *activation* of the right (lesioned) parietal cortex via anodal tDCS also improved leftsided target detection. Finally, lesion size correlated negatively with the beneficial effect of tDCS on neglect, indicating the strongest effects in patients with smaller lesions. This study elegantly demonstrates the concept of interhemispheric competition, originally formulated by Kinsbourne (1977) for spatial attentional processes by using the method of biparietal tDCS.

Although this idea of interhemispheric (im)balance or rivalry is well established in motor research (cf. Nowak, Grefkes, Ameli, & Fink, 2009) it has only rarely been investigated in attentional and neglect research. This is surprising, given the early description of this concept by Kinsbourne (1977) and abundant animal research on neglect in cats favouring such an interhemispheric account of neglect. Rushmore, Valero-Cabre, Lomber, Hilgetag, and Payne (2006) have shown in a series of experiments, that unilateral cooling deactivation of the cat's (i.e. right) perisylvian cortex results in leftsided visual neglect. However, subsequent cooling of the contralateral (i.e. left) mirror-symmetric cortex to the same temperature restores normal orienting behaviour. Further cooling of the left perisylvian cortex to an even lower temperature induces then *rightsided* visual neglect, which can again be cancelled by subsequent cooling of the right perisylvian cortex to the same temperature, and so on. These results – as exciting as they are – have so far had only little impact on human neglect models. Most of the models of human neglect assume some intrahemispheric (mostly right-hemispheric) deficient mechanism that is related to certain (parieto-temporal, subcortical) brain areas or disrupted fibre pathways such as the superior longitudinal fasciculus (Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007) of the damaged hemisphere. Treatment approaches derived from such models therefore strive to activate this damaged hemisphere with different stimulation techniques, i.e. prism adaptation, optokinetic stimulation, attentional training, neck-muscle-vibration or related approaches (for review see Chokron, Dupierrix, Tabert, & Bartolomeo, 2007; Kerkhoff, 2003). Treatment approaches derived from a model of dysfunctional interhemispheric competition in unilateral (i.e. leftsided) neglect would suggest that the intact (left) hemisphere is hyperactive and the lesioned (right) hemisphere hypoactive. Consequently, three potential ways of intervention could reduce this leftsided neglect: (a) deactivation of the hyperactive left hemisphere; (b) activation of the hypoactive right hemisphere, and (c) a combination of both. A recent study by Nyffeler, Cazzoli, Hess, and Muri (2009) impressively illustrates the potential of this different treatment approach. The authors tested whether a deactivation of the intact (left) parietal cortex *via* repetitive TMS (theta-burst-stimulation) induces long-lasting recovery from spatial neglect. In their study they found that two stimulation sessions over the intact parietal cortex led to a reduction of left spatial neglect for 8 h, while 4 stimulation sessions prolonged this therapeutic effect up to 32 h. This encouraging result could possibly be also achieved by the technically much less demanding technique of repetitive parietal tDCS or GVS (see below).

Another interesting avenue for further research in this field is to assess the effect of *combined* parietal tDCS and sensory stimulation techniques known to alleviate neglect such as optokinetic stimulation, prism adaptation or attentional training. As tDCS (and probably also GVS) produce clear aftereffects (see Section 3 of this review) it could significantly augment and prolong the therapeutic effects of such neglect treatments, without requiring additional time, which by themselves are still too ineffective to enable full independence or even return to work in neglect patients (Bowen & Lincoln, 2007).

7. Effects of Galvanic Vestibular Stimulation

So far, very few studies have dealt with GVS in the field of neuropsychology (summarized in Table 4). The *behavioural* effects of

Table 3
Selection of studies using tDCS of the parietal cortex in healthy subjects or patients.

Reference	Type of study	Position of electrodes	Stimulation parameters	Population	Effects
(a) Somatosensory cortex					
Dieckhofer et al. (2006)	Modulation study	16 electrodes over the somatosensory cortex and 16 electrodes over the contralateral forehead	1 mA for 9 min, 2 sessions, anodal vs. cathodal	10 healthy subjects	Decrease of low-frequency components of SEPs by cathodal stimulation lasting for 60 min after the end of stimulation
Matsunaga et al. (2004)	Modulation study	Left motor cortex: over the central field of the right abductor pollicis brevis muscle and above the contralateral orbita	1 mA for 10 min, 2 sessions, anodal vs. cathodal	8 healthy subjects	Increase of SEPs by anodal stimulation lasting for 60 min after the end of stimulation
Ragert et al. (2008)	Sham-controlled modulation study	Over C3′, 2 cm posterior to C3[a] and above the contralateral orbita	1 mA for 20 min, 2 sessions, anodal vs. sham	10 healthy subjects	Improvement of spatial tactile acuity by anodal stimulation lasting for 40 min after the end of stimulation
Rogalewski et al. (2004)	Sham-controlled modulation study	Over C4[a] and above the contralateral orbita	1 mA for 7 min, 3 sessions, anodal vs. cathodal vs. sham	13 healthy subjects	Disruption of tactile discrimination of vibratory stimuli by cathodal stimulation lasting for 7 min after the end of stimulation
(b) Posterior parietal cortex					
Sparing et al. (2009)	Sham-controlled modulation study	Left parietal cortex (P3[a]) vs. right parietal cortex (P4[a])	57 μA for 10 min, 3 sessions, anodal vs. cathodal vs. sham	20 healthy subjects; 10 patients with leftsided visual neglect	Healthy subjects: anodal stimulation enhanced visual target detection in contralateral visual hemifield, cathodal stimulation depressed it. Neglect patients: anodal stimulation of right parietal cortex improved target detection in left visual hemifield; cathodal stimulation of left parietal cortex improved target detection in left visual hemifield.
Stone and Tesche (2009)	Sham-controlled modulation study	Left parietal cortex (P3[a])	2 mA for 20 min, 3 sessions: anodal vs. cathodal vs. sham	14 healthy subjects	Cathodal stimulation impaired attention switches from local to global visual processing; Anodal stimulation impaired local-to-global switching for at least 20 min post-stimulation

SEPs: somatosensory evoked potentials.
[a] According to the international 10/20 EEG System.

anodal GVS in healthy subjects include a slight ipsiversive ocular tilt reaction of 0.5–3.7° (Zink, Steddin, Weiss, Brandt, & Dieterich, 1997), a modest perceptual tilt of the subjective visual and tactile vertical in the roll plane (Mars, Popov, & Vercher, 2001) and a sensation of lateral or rotational self-motion (with higher current intensities) which is often viewed as a core sign of vestibular stimulation induced by GVS (Stephan et al., 2005).

Two recent studies have investigated the influence of GVS on cognitive functions in healthy subjects. Wilkinson and colleagues (Wilkinson, Nicholls, Pattenden, Kilduff, & Milberg, 2008) showed that subsensory anodal stimulation over the left mastoid speeds visual memory recall of faces. Lenggenhager, Lopez, and Blanke (2008) showed in healthy subjects increased response times in a mental transformation task during anodal right-mastoid, but not during anodal left-mastoid GVS. Interestingly, this disrupting effect was only evident in subjects using an egocentric transformation strategy (that is, they imagined turning themselves) to solve the task, and not in those subjects using an allocentric strategy (imagining that the environment is rotated; Lenggenhager et al., 2008). This study therefore suggests that GVS seems to act more on ego- rather than allocentric spatial cognition, and neatly illustrates the interaction of the physiological stimulation with individual processing strategies.

Fink et al. (2003) showed in healthy subjects the effect of GVS on horizontal line bisection and related it to significant activations in the right parietal and frontal cortex during cathodal GVS of the right mastoid.

Clinical studies with parietally lesioned patients show a strong influence of GVS on a variety of multimodal spatial cognition tasks, including neglect, which is in agreement with the multisensory properties of the activated vestibular cortical areas outlined above. Rorsman, Magnusson, and Johansson (1999) showed in an early pioneering study the effects of subliminal GVS on the line cancellation task in 14 patients suffering from visual-spatial neglect. With the anode on the left and the cathode on the right mastoid, the authors showed an improvement of target detection in the left hemifield of the line crossing task during GVS. Saj, Honore, and Rousseaux (2006) showed that left-cathodal GVS improved the contraversive tilt of the subjective visual vertical in patients with a right hemispheric lesion, whereas right-cathodal stimula-

Table 4
Selection of studies using Galvanic Vestibular Stimulation (GVS) in healthy subjects or neurological patients.

Reference	Type of study	Position of electrodes	Stimulation parameters	Population	Effects
Fink et al. (2003)	Modulation study	One electrode on the left and the other on the right mastoid	2–3 mA for periods of 24 s (rise time of 2 mA/s), left-anodal/right-cathodal vs. right-anodal/left-cathodal	12 healthy subjects	Activations (as indicated by fMRI) in the right posterior parietal and ventral premotor cortex when performing a horizontal line bisection task during left-anodal/right-cathodal GVS
Lenggenhager et al. (2008)	Sham-controlled modulation study	Two electrodes at both mastoids (one anode, one cathode) + 2 reference electrodes 5 cm below at the neck	1.0 mA (±0.2 mA) for epochs of 10 or 15 s during task performance	11 healthy subjects	A: slight tilt of visual vertical towards the anode B: Increase of response times in a mental transformation task during right-anodal/left-cathodal stimulation → impairment of mental transformation by GVS but only in subjects using an ego-centric vs. object-centric processing strategy
Mars et al. (2001)	Modulation study	One electrode on the left and the other on the right mastoid	1.25 mA, 2.5 mA left-anodal/right cathodal vs. right-anodal/left-cathodal vs. no stimulation	14 healthy subjects	Tilt of the visual and haptic vertical in the frontal plane towards anode; larger tilts with higher current intensity
Rorsman et al. (1999)	Sham-controlled modulation study	Anode on the left and cathode on the right mastoid	Subsensory stimulation (median 1.15 mA); left-anodal/right-cathodal vs. sham	14 stroke patients with left-sided neglect	Improvement of target detection in the left hemifield of the line-crossing task during left-anodal/right-cathodal stimulation
Saj et al. (2006)	Sham-controlled modulation study	One eletrode on the left and the other on the right mastoid	1.5 mA; left-anodal/right-cathodal vs. right-anodal/left-cathodal vs. sham	12 patients with right-hemispheric lesions and 8 healthy individuals	Reduction of the contraversive tilt of the subjective visuo-haptic vertical in patients with right-hemispheric lesions, especially when neglect was present
Wilkinson et al. (2008)	Sham-controlled modulation study	One eletrode on the left and the other on the right mastoid	Subsensory, noise-enhanced stimulation; Subsensory, constant stimulation (mean: 0.8 mA)	Exp. 1: 12 healthy subjects Exp. 2: 12 healthy subjects	Speeding up of visual memory recall of faces during left-anodal/right-cathodal stimulation (reaction-time decrease by 0.5 s)
Zink et al. (1997)	Modulation study	One eletrode on the left and the other on the right mastoid	1.5–3 mA seven times at 10 s intervals, unipolar stimulation	12 healthy individuals	Ipsiversive ocular torsion (0.5–3.7°), a contralateral tilt of the peripheral visual field (1–9°) and of a foveal vertical line (0.5–6.2°) during anodal stimulation of the right mastoid

tion aggravated the tilt, but to a lesser extent. These modulatory effects were larger in patients with neglect compared with right-brain damaged patients without neglect.

Fig. 4 shows the effects of GVS on horizontal line bisection in patients with leftsided visual neglect following right cerebral brain lesions. Left cathodal GVS leads to a nearly full normalization of the initial rightward deviation in line bisection (Oppenländer et al., unpublished observations) typically observed in these patients (Fink et al., 2003). A similar effect was seen on cancellation performance in the same patient group (see Fig. 4B) as well as in the perception of the subjective visuo-haptic vertical in right brain damaged patients (Fig. 4C; Oppenländer et al., unpublished observations). Although this online-effect is temporary it would be interesting to evaluate repetitive, multi-session GVS in such patients. In accordance with other sensory stimulation techniques (Kerkhoff, 2003) such as optokinetic stimulation (Kerkhoff, Keller, Ritter, & Marquardt, 2006), transcutaneous electric stimulation (Pizzamiglio, Vallar, & Magnotti, 1996; Schroder, Wist, & Homberg, 2008), or head-on-trunk rotation (Schindler & Kerkhoff, 1997) the prediction would be that repetitive GVS could induce a permanent, though perhaps partial, recovery of line bisection or cancellation deficits in neglect patients.

A phenomenon which is often associated with the neglect syndrome and occurs quite often after unilateral right- or leftsided cortical damage is extinction. In extinction, the patient is unimpaired in the processing of a stimulus presented *unilaterally* to the right or left side but shows a contralateral processing deficit when stimuli are presented simultaneously on both sides (Bender, 1977). This phenomenon can be significantly modulated by peripheral repetitive magnetic stimulation of the hand (Heldmann, Kerkhoff, Struppler, Havel, & Jahn, 2000). Fig. 4D shows findings from a patient with chronic leftsided tactile extinction caused by an intracerebral bleeding into the superior parietal region of the right hemisphere (lesion age: 5 years). Left cathodal GVS but not sham or right cathodal stimulation reduced leftsided tactile extinction by 40% as compared with baseline (Kerkhoff, Dimova, & Utz, unpublished observations).

Other disorders of spatial cognition frequently observed in patients with brain damage are constructional apraxia (Grossi & Trojano, 2001) and impaired spatial navigation (de Renzi, 1982). Patients with neglect and spatial cognition deficits are also often unaware of their neurological impairments such as a contralesional hemiparesis (Karnath, Baier, & Nagele, 2005). Given the knowledge of GVS-induced activations in brain areas such as the supramarginal

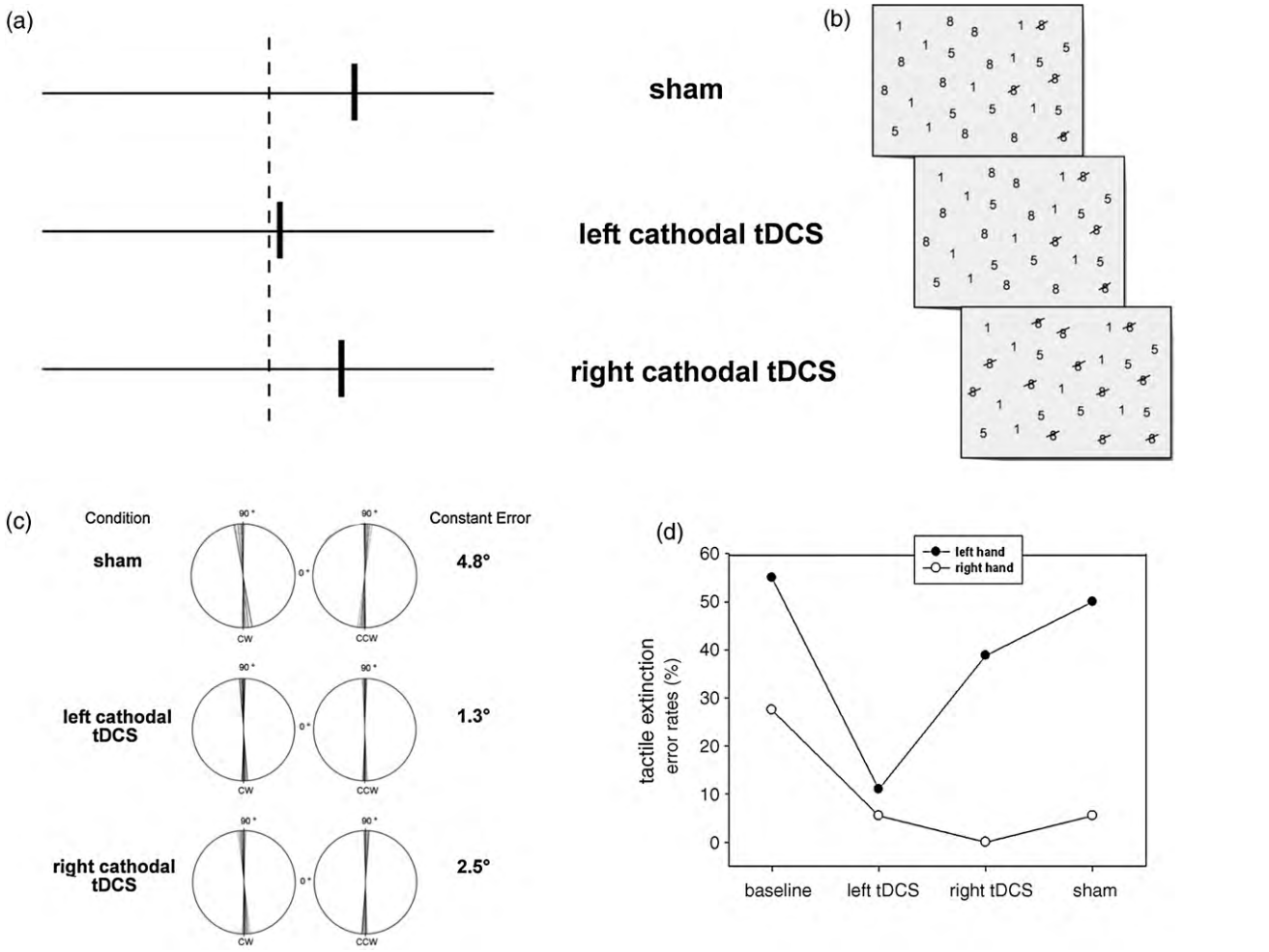

Fig. 4. Illustration of the effects of Galvanic Vestibular Stimulation (tDCS of the mastoids behind the ears) on different aspects of spatial cognition. (A) Effect of tDCS on horizontal line bisection. Left-cathodal stimulation normalizes the typical rightward bias of patients with leftsided visual neglect, while right-cathodal stimulation has no effect when compared with the baseline. (B) Effects of tDCS on cancellation performance in a patient with leftsided visual neglect. Right-cathodal stimulation improved cancellation performance, while left-cathodal stimulation had no significant effect when compared with sham-stimulation (electrodes mounted, but no current delivered). (C) Effect of tDCS on the judgment of the subjective visual vertical in patients with unilateral right-hemispheric brain lesions. During left cathodal stimulation the contralesional tilt of the visual vertical typically observed in these patients (Kerkhoff, 1999) is transiently normalized (data presented in A, B, C: Oppenländer et al., unpublished observations). (D) Improvement of leftsided tactile extinction in a chronic patient with a right parietal lesion and severe leftsided tactile extinction. Note the significant reduction of leftsided tactile extinction errors (see arrow) during left-cathodal stimulation at the mastoid, while sham tDCS or right cathodal tDCS had no effect (data from Kerkhoff, Dimova, & Utz, unpublished observations).

gyrus and the posterior insula it might be promising to evaluate modulatory effects of GVS on neuropsychological deficits, such as neglect, extinction, spatial cognition deficits and unawareness. Future studies addressing these research questions could not only help to uncover a possible "vestibular" influence on these neuropsychological disorders but also identify novel and more effective treatment techniques for affected patients.

8. Effects of tDCS on mood, pain and cognitive functions

8.1. Mood

The idea of treating mood disorders with tDCS is not new since Aldini, as stated before, used this technique in 1804 to treat melancholic patients successfully. When tDCS had its comeback in the 1960s, Costain, Redfearn, and Lippold (1964) conducted a controlled double-blind trial with 24 depressed patients (see summary in Table 5a). The anode was placed over each eyebrow and the cathode on the leg and a current of 0.25 mA was delivered on several days, each session lasting for 8 h. The authors reported an antidepressant effect of the stimulation as indicated by psychiatrists' and nurses' ratings as well as self-ratings. Recently, Koenigs, Ukueberuwa, Campion, Grafman, and Wassermann (2009) reexamined this technique of bilateral frontal tDCS with an extra-cephalic electrode in 21 healthy individuals and concluded that it had no effect on affect, arousal, emotional state, emotional decision-making or psychomotor functions. In another study, stimulation with bilaterally attached electrodes at fronto-cortical sites and on the mastoids led to an improvement of mood after stimulation during wake intervals and during sleep (Marshall, Molle, Hallschmid, & Born, 2004).

Fregni, Boggio, Nitsche, Marcolin, et al. (2006) investigated the effects of repeated stimulation on major depression. In a controlled, randomized double-blind trial, they treated 10 patients with anodal stimulation of the left DLPFC. A total of 5 sessions distributed over 9 days were provided. The scores in the Beck Depression Inventory and the Hamilton Depression Rating Scale in the treatment group decreased significantly as compared with their baseline scores. Boggio, Rigonatti, et al. (2008) reported effects lasting for 4 weeks after 10 sessions (during 2 weeks) of anodal stimulation over the left DLPFC in 40 medication-free patients suffering from major depression.

Table 5
Selection of studies investigating the effects of tDCS on mood (a), pain (b) and cognitive functions (c) in healthy subjects or patients.

Reference	Type of study	Position of electrodes	Stimulation parameters	Population	Effects
(a) Mood					
Boggio et al. (2007)	Randomized, double-blind, sham-controlled	Left DLPFC: anode over F3[a]; occipital cortex: anode placed on the midline and 2 cm above the inion; cathode over the left supraorbital area in each case	2 mA for 20 min/day on 10 days, anodal vs. sham	26 patients with major depression	Improvement in an affective go-no-go task after 1 session anodal stimulation of the left DLPFC; no correlation with mood changes after 10 stimulation sessions
Boggio, Rigonatti, et al. (2008)	Randomized, double-blind, sham-controlled	Left DLPFC: anode over F3[a]; occipital cortex: anode placed on the midline and 2 cm above the inion; cathode over the left supraorbital area in each case	2 mA for 20 min/day on 10 days, anodal left prefrontal vs. anodal occipital vs. sham	40 patients with major depression	Reduction of Scores in the Beck Depression Inventory and Hamilton Depression Rating Scale after anodal prefrontal stimulation; stable for 4 weeks after end of intervention
Boggio et al. (2009)	Randomized, double-blind, sham-controlled, cross-over	M1: anode over C3[a], DLPFC: anode over F3[a], occipital cortex: anode over Cz[a], cathode over the contralateral suborbital area in each case	2 mA for 5 min, 4 sessions, anodal motor cortex vs. anodal DLPFC vs. anodal occipital cortex vs. sham	23 healthy subjects	Reduction of discomfort and unpleasantness ratings of aversive pictures during DLPFC stimulation
Costain et al. (1964)	Randomized, double-blind, sham-controlled, cross-over	Anodes placed over each eyebrow and cathode on one leg	0.25 mA for 8 h/day over 12 days, anodal vs. sham	24 depressed patients	Antidepressant effect psychiatrists' and nurses' ratings and self-ratings
Fregni, Boggio, Nitsche, Marcolin, et al. (2006)	Randomized, double-blind, sham-controlled	Left DLPFC, anode placed over F3[a], cathode over the contralateral supraorbital area	1 mA for 20 min/day on 5 days, anodal vs. sham	10 patients with major depression	Decrease of Scores in the Beck Depression Inventory and Hamilton Depression Rating Scale after anodal stimulation
Koenigs et al. (2009)	Double-blind, sham-controlled, cross-over	Two electrodes placed on the forehead over F_{p1}[a] and F_{p2}[a] and one on the non-dominant arm	2.5 mA for 35 min, 3 sessions, anodal vs. cathodal vs. sham	21 healthy subjects	No effect on affect, arousal, emotional state, emotional decision-making and psychomotor functions
Marshall et al. (2004)	Double-blind, sham-controlled, cross-over	Bilateral fronto-lateral, anodes over F3[a] and F4[a] and cathodes at the mastoids	0.26 mA/cm^2 intermittently stimulation (15 s on, 15 s off) for 30 min during sleep and wakefullness, 2 sessions, anodal vs. sham (double-blind, cross-over)	30 healthy men	Improvement of mood after stimulation during wake intervals and during sleep
(b) Pain					
Antal et al. (2008)	Sham-controlled modulation study	One electrode over the left S1[b] and the other electrode over the right eyebrow	1 mA for 15 min, 3 sessions, anodal vs. cathodal vs. sham	10 healthy subjects	Decrease in perceived pain intensity and in the amplitude of N2 component under laser stimulation of the contralateral hand to the side of tDCS after cathodal stimulation
Boggio, Zaghi, et al. (2008)	Double-blind, randomized, sham-controlled modulation study	M1: anode over C3[a], DLPFC: anode over F3[a], V1: anode over Oz[a]; cathode over the contralateral supraorbital area in each case	2 mA for 5 min, 2 sessions, anodal vs. sham	20 healthy subjects	Increase in perception and pain thresholds during anodal stimulation of M1; increase in pain threshold during anodal stimulation of DLPFC; no effect for occipital anodal or sham stimulation
Chadaide et al. (2007)	Sham-controlled modulation study	One electrode over occipital cortex at Oz[a] and other electrode at Cz[a]	1 mA for 10 min, 3 sessions, anodal vs. cathodal vs. sham	16 migraine patients with and without aura; 9 healthy subjects	Decrease in phosphene thresholds in migraine patients as in the healthy subjects after anodal stimulation; larger effect in migraine patients with aura

Table 5 (*Continued*)

Reference	Type of study	Position of electrodes	Stimulation parameters	Population	Effects
Fregni, Boggio, Lima, et al. (2006)	Double-blind, randomized, sham-controlled, parallel-group treatment study	M1: anode over C3/C4[a] (for patients with asymmetric pain contralateral M1; for patients with symmetric pain the dominant left M1); cathode over the contralateral supraorbital area; sham stimulation of M1	2 mA for 20 min/day on 5 consecutive days	17 patients with central pain after traumatic spinal cord injury	Improvement in pain intensity ratings after treatment with anodal stimulation over M1; no adverse effects on cognitive functions; duration of effects: no significant effects at 16 days-follow-up
Fregni, Gimenes, et al. (2006)	Double-blind, randomized, sham-controlled, parallel-group treatment study	M1: anode over C3[a] (for patients with asymmetric pain contralateral M1; for patients with symmetric pain the dominant left M1), left DLPFC: anode over F3[a]; cathode over the contralateral supraorbital area; sham stimulation of M1	2 mA for 20 min/day on 5 consecutive days	32 female patients with fibromyalgia	Improvement in pain ratings after treatment with anodal stimulation over M1; mild adverse effects after both active stimulation as well as after sham stimulation; duration of effects: lasting effects at 3-week-follow-up
Roizenblatt et al. (2007)	Double-blind, randomized, sham-controlled, parallel-group treatment study	M1: anode over C3[a] (for patients with asymmetric pain contralateral M1; for patients with symmetric pain the dominant left M1), left DLPFC: anode over F3[a]; cathode over the contralateral supraorbital area; sham stimulation of M1	2 mA for 20 min/day on 5 consecutive days	32 female patients with fibromyalgia	Increase in sleep efficacy and delta activity in non-REM sleep after M1 anodal stimulation; decrease in sleep efficacy, and increase in REM and sleep latency after DLPFC anodal stimulation; improvement in clinical parameters associated with increase in sleep efficacy after M1 stimulation
(c) Cognitive functions					
Beeli et al. (2008)	Modulation study	Left and right DLPFC: over F3[a] or F4[a] and on the ipsilateral mastoid	1 mA for 15 min, 2 sessions, anodal vs. cathodal	24 male subjects	More cautious driving behaviour in a driving simulator after anodal stimulation
Boggio, Ferrucci, et al. (2006)	Single-blind, sham-controlled modulation study	Left DLPFC: anode over F3[a]; Motor Cortex: anode over M1; cathode over the contralateral right orbit in each case	1 mA (study 1) and 2 mA (study 2) for 20 min, 3 sessions, anodal DLPFC vs. anodal M1 vs. sham	18 patients with Parkinson's disease	Improved accuracy in performance during a three back working memory task by anodal tDCS of the left DLPFC with 2 mA
Boggio, Khoury, et al. (2008)	Single-blind, sham-controlled modulation study	Left DLPFC: anode over F3[a]; left temporal cortex: anode over T7[a]; cathode over the right supraorbital area in each case	2 mA for 30 min, 3 sessions, anodal left DLPFC vs. anodal left temporal cortex vs. sham	10 patients with Alzheimer's disease	Improved performance in an visual recognition memory task during anodal stimulation over the left DLPFC and the left temporal cortex
Fecteau et al. (2007)	Randomized, single-blind, sham-controlled modulation study	Left and right DLPFC: anode over F3[a] and cathode over F4[a] and vice versa (study 1); anode over F3[a] or over F4[a] and cathode over the contralateral orbita (study2)	2 mA < 20 min, 1 session, anodal vs. cathodal vs. sham	35 healhty subjects	Reduction in risk-taking behaviour during bilateral stimulation of the left or right DLPFC (with the cathode over the contralateral DLPFC)

Ferrucci, Mameli, et al. (2008)	Blinded subjects and observer, sham-controlled modulation study	Bilateral temporoparietal: over P3[a]–T5[a] (left side), P6[a]–T4[a] (right side) and over the right deltoid muscle	1.5 mA for 15 min, 3 sessions, anodal vs. cathodal vs. sham	10 patients with probable Alzheimer's disease	Anodal stimulation improved the accuracy in a word recognition memory task 30 min post-stimulation, whereas cathodal stimulation decreased performance
Ferrucci, Marceglia, et al. (2008)	Single-blind, sham-controlled modulation study	Cerebellum: 2 cm under the inion, 2 cm posterior to the mastoid process and over the right deltoid muscle; prefrontal corex: between F_{p1}[a] and F3[a] (left side) and between F_{p2}[a] and F4[a] (right side) and over the right deltoid muscle	2 mA for 15 min, 3 sessions, anodal vs. cathodal vs. sham	13 healthy subjects	Disruption of the practice-dependent improvement in reaction times during a modified Sternberg verbal memory task 35 min after anodal and cathodal cerebellar tDCS
Fregni, Boggio, Nitsche, et al. (2005)	Single-blind, sham-controlled modulation study	Left DLPFC: anode over F3[a], cotor cortex: anode over M1, cathode over the contralateral suborbital area in each case	1 mA for 10 min, 2 sessions, anodal vs. cathodal	15 healthy individuals	Improved accuracy of performance during a sequential-letter working memory task during anodal stimulation over the left DLPFC
Fregni, Boggio, Nitsche, Riganotti, et al. (2006)	Blinded subjects and observer, randomized, sham-controlled treatment study	Left DLPFC: anode over F3[a], cathode over the contralateral suborbital area	1 mA for 20 min/day on 5 alternate days, anodal vs. sham	18 patients with major depression	Improvement in a digit-span (forward and backward) task
Kincses et al. (2004)	Randomized modulation study	Occipital cortex: over Oz[a] and Cz[a]; left prefrontal cortex: over F_{p3}[a] and Cz[a]	1 mA for 10 min, 3 sessions, anodal vs. cathodal	22 healthy individuals	Improvement of implicit classification learning during anodal stimulation of the left prefrontal cortex
Marshall et al. (2004)	Double-blind, sham-controlled cross-over modulation study	Bilateral fronto-lateral, anodes over F3[a] and F4[a] and cathodes at the mastoids	0.26 mA/cm^2 intermittently stimulation (15 s on, 15 s off) for 30 min during sleep and wakefullness, 2 sessions, anodal vs. sham	30 healthy men	Improved retention of word pairs after anodal stimulation during periods rich in slow-wave sleep
Marshall et al. (2005)	Double-blind, sham-controlled cross-over modulation study	Bilateral fronto-lateral, anodes over F3[a] and F4[a] and cathodes at the mastoids	0.26 mA intermittently stimulation (15 s on, 15 s off) for 15 min, 3 sessions, anodal vs. cathodal vs. sham	12 healthy individuals	Impaired response selection and preparation in a modified Sternberg task during anodal and cathodal stimulation

S1: primary somatosensory cortex; M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; V1: primary visual cortex.

[a] According to the international 10/20 EEG System.

[b] According to Talairach coordinates.

Furthermore, a single session of anodal tDCS of the left DLPFC combined with cathodal stimulation of the frontopolar cortex improved the performance in an affective go-no-go task in 26 patients with major depression, but only for pictures containing positive emotions. No significant correlation with mood changes that were assessed after 10 treatments with tDCS was obtained. The authors conclude that the left DLPFC plays a role in the processing of *positive* emotions but that the effects of tDCS on cognition and mood in major depression are independent of each other (Boggio et al., 2007).

A study investigating the effects of tDCS on emotions associated with pain revealed a reduction of discomfort and unpleasantness ratings of aversive pictures during tDCS over the DLPFC. These results suggest that the DLPFC is involved in emotional pain processing and that different pathways are critical in tDCS-evoked modulation of pain-related emotions and somatosensory pain perception (Boggio, Zaghi, & Fregni, 2009). Table 5 summarizes the studies concerning the effects of tDCS on mood, pain and cognitive functions.

8.2. Pain

Antal et al. (2008) demonstrated beneficial effects on acute pain perception after DC stimulation applied over the somatosensory cortex in 10 healthy subjects (see Table 5b). The effects on pain perception were assessed in terms of pain intensity ratings and EEG components that were related to the induction of pain by laser stimulation (N1, N2 and P2 components). Only cathodal tDCS showed significant effects (behavioural and EEG) while anodal and sham tDCS were ineffective. Moreover, differential effects on nociception in healthy subjects arising from different stimulation sites were reported by Boggio, Zaghi, et al. (2008). Three different application conditions with anodal and cathodal tDCS were investigated: over the primary M1, DLPFC and over the occipital cortex (V1). The perception threshold and the pain threshold evoked by peripheral electrical stimulation of the right index finger were measured as outcome parameters. The greatest effects were found after anodal stimulation of M1 (the motor cortex in the hemisphere related to the stimulated finger), a marginal significant effect for the pain threshold after anodal tDCS over DLPFC, but no effect of V1 stimulation.

Chadaide et al. (2007) investigated the effects of tDCS on migraine. Migraine may be – at least in some forms – because of an overexcitability of the visual cortex. This can be assessed by measuring the threshold of TMS stimulation intensity necessary to produce phosphenes (light sensations after TMS). Using tDCS (1 mA for 10 min over the visual cortex at Oz, other electrode at Cz) Chadaide et al. (2007) revealed changes in such phosphene thresholds. Anodal tDCS had the highest impact in migraine patients with aura: they showed a *decrease* in the phosphene threshold due to the increase in cortical excitability as measured by TMS. In contrast, cathodal tDCS showed no effect in migraine patients with or without aura. In healthy subjects cathodal tDCS increased the phosphene threshold, which indicates a reduction in cortical excitability as measured by TMS.

In another clinical population, Fregni, Boggio, Lima, et al. (2006) studied patients with central pain after traumatic spinal cord injury. They demonstrated therapeutic effects of anodal tDCS over M1. The treatment procedure included 20 min of 2 mA tDCS for 5 consecutive days. For patients with symmetric pain on both body sides, the anode was placed over the dominant left M1, for those with asymmetric pain it was placed over the contralateral M1. Significant reductions were obtained in ratings of pain intensity after 5 sessions. This beneficial effect did not covary with changes in anxiety or depression during the treatment. Effects did not reached significance at 16-days-follow-up as compared to baseline.

Fregni, Gimenes, et al. (2006) used the same stimulation setup in patients with fibromyalgia. Fibromyalgia is a chronic disease with the following symptoms: pain in all areas of the body, generalized weakness, neurological symptoms, attention and sleep deficits, chronic fatigue and a general reduction of physical and mental capacities. Two different real tDCS conditions were compared: anodal tDCS of the primary motor cortex (same application procedure as Fregni, Boggio, Lima, et al., 2006) and anodal tDCS of the left DLPFC, as well as sham stimulation over M1. The greatest effects were seen for anodal tDCS of M1, which is in accordance with the findings reviewed above. Finally, Roizenblatt et al. (2007) studied the same sample as Fregni, Gimenes, et al. (2006) and investigated the effects of anodal tDCS of M1 and anodal tDCS of the DLPFC on sleep and pain parameter in patients with fibromyalgia. Increase in sleep efficacy associated with improvement in clinical parameters was assessed after anodal stimulation of M1. Here again, the greatest reduction in pain intensity was found after anodal stimulation of M1.

The findings reviewed above may suggest a variety of different mechanisms related to the modulation of pain. So far, beneficial effects of tDCS are mostly associated with anodal stimulation of the primary motor cortex, suggesting not a strong focal but rather a connectivity-based mechanism of action of tDCS on pain syndromes. Other relevant pain syndromes might be interesting for tDCS research such as thalamic pain syndrome or low back pain.

In conclusion, tDCS provides an interesting technique for pain research – both from an experimental and a clinical perspective. Furthermore, the different components of pain (physiological, emotional, attentional, pain-memory) could suggest different directions for future research in this relevant area.

8.3. Cognitive functions

The results of studies investigating the influence of tDCS on cognitive functions show facilitating as well as inhibitory effects (see Table 5c). For instance, anodal stimulation of the DLPFC improved the accuracy of performance during a sequential-letter working-memory task in healthy subjects (Fregni, Boggio, Nitsche, et al., 2005), in a three-back working memory task in patients with Parkinson's disease (Boggio, Ferrucci, et al., 2006) and in a digit-span (forward and backward) task in patients with major depression after five daily stimulation sessions (Fregni, Boggio, Nitsche, Rigonatti, et al., 2006). In another study, Ferrucci, Marceglia, et al. (2008) showed that anodal and cathodal tDCS over the cerebellum disrupted the practice-dependent improvement in the reaction times during a modified Sternberg verbal working-memory task. Furthermore intermittent bilateral tDCS at frontocortical electrode sites during a modified Sternberg task impaired response selection and preparation in this task (Marshall, Molle, Siebner, & Born, 2005).

Further effects of tDCS on cognitive functions were shown by Kincses, Antal, Nitsche, Bartfai, and Paulus (2004) who demonstrated that anodal, but not cathodal stimulation over the left prefrontal cortex improved implicit classification learning. Moreover, bilateral tDCS over the left or the right DLPFC (with the cathode over the contralateral DLPFC) reduced risk-taking behaviour (Fecteau et al., 2007). In a related study, Beeli and colleagues (Beeli, Koeneke, Gasser, & Jancke, 2008) recently found that anodal tDCS over the left and the right DLPFC (with the cathode over the ipsilateral mastoid) evoked more cautious driving in normal subjects placed in a driving simulator.

Marshall et al. (2004) investigated the effects of tDCS, delivered during sleep, on verbal memory. They showed that bilateral anodal tDCS at frontocortical electrode sites during sleep periods rich in slow wave sleep improved the retention of word pairs. This was not observed during wakefulness.

In a clinical study with patients suffering from Alzheimer's disease Ferrucci, Mameli, et al. (2008) tested the effects of tDCS on a word recognition memory task. Current was delivered bilaterally by two direct current stimulation devices, whereby one electrode of each device was placed over the temporoparietal areas and the other electrodes over the right deltoid muscle. Anodal stimulation improved, whereas cathodal stimulation decreased, memory performance in the patients.

Boggio, Khoury, et al. (2008) also showed effects of tDCS on a memory task in patients with Alzheimer's disease. Anodal stimulation over the left DLPFC as well as over the left temporal cortex improved the performance in a visual recognition memory task, which was not because of an enhancement in attention. However, since the second electrode was placed over the right supraorbital area, the improvements might also be the result of the stimulation of this area.

In summary tDCS modulates many aspects of cognition, both in healthy subjects and clinical populations. Surprisingly few studies have so far been conducted to evaluate the effects of tDCS on different aspects of attention (selective, sustained, divided). This might be an interesting field for future research.

9. Discussion, conclusions and future directions

The reviewed studies show that tDCS and GVS are attractive, easy-to-use and relatively safe methods for neuroscientific research. In comparison with TMS, tDCS is technically less demanding, induces similar aftereffects, but is less focal in its mechanism of action. tDCS induces online-effects and in some cases also longer lasting aftereffects in a great variety of sensory, motor, cognitive and emotional domains, both in healthy subjects and in different clinical populations. Both facilitation and inhibition of function is possible and has been shown. What are the most promising directions for future research in the next 5–10 years?

9.1. Sensory and motor processing

Many applications of tDCS in the visual, auditory and haptic modality, or even in olfaction and taste are conceivable, both in healthy subjects and patients. In vision research and vision rehabilitation the "old" idea of a visual prosthesis (Brindley & Lewin, 1968) or a vision-substitution system (Bach-y-Rita, 1983) for blind subjects or patients with cortical visual field defects may be revitalized with tDCS. In fact, visual prostheses are currently investigated as retinal implants or as brain–computer interfaces (Andersen, Burdick, Musallam, Pesaran, & Cham, 2004). In a similar vein, occipital or parietal tDCS might be employed as a permanent stimulation prosthesis for patients with visual field defects or spatial neglect, respectively. Similar ideas might be applicable in the haptic and auditory modality where only few studies regarding the effects of tDCS are currently available.

In motor research, motor cognition and motor rehabilitation tDCS has already shown its usefulness. Studies in healthy subjects show a significant effect of anodal stimulation on isometric force endurance and a smaller muscular fatigue effect. This may be an interesting starting point for applications in sports medicine, ageing subjects and neurological patients suffering from rapid fatigue. Anodal tDCS improves motor capacities in stroke patients with hemiparesis (Hummel & Cohen, 2005), and may also be helpful for patients with postural disorders which occur frequently after right-hemisphere stroke (Perennou et al., 2008). Furthermore, tDCS might be a useful technique for the adjuvant treatment of disorders such as apraxia, optic ataxia and non-visual ataxia, for which only few or no effective treatments (in the case of optic ataxia) are currently available.

9.2. Spatial-attentional and nonspatial attentional processing

In the domain of multimodal spatial cognition and spatial neglect tDCS or GVS, both may constitute easily applicable tools suitable to modulate vestibular-cortical functions and related spatial-attentional capacities without inducing significant nystagmus and vertigo as typically observed during caloric-vestibular stimulation (CVS). In the same vein, subliminal ("unconscious") or sham stimulation is much easier to realize than with TMS or CVS. As already suggested in Section 7, GVS might also be used to investigate the potential "vestibular" contributions to a variety of neuropsychological disorders that include a spatial component. These might include constructional apraxia, where early studies suggest a vestibular contribution based on lesion localization and clinical signs (Hecaen, Penfield, Bertrand, & Malmo, 1956). Another such topic may be the multifaceted disorders of body cognition (Frederiks, 1969; Goldenberg, 2001; Groh-Bordin et al., 2009) where the same idea might be pursued.

However, another interesting focus of research is nonspatial attentional functions. Recent studies have found that the right inferior parietal lobe is also involved in nonspatial attentional functions, and this in a multimodal way (for review see Husain & Rorden, 2003). GVS could be tested for its effects on such nonspatial attentional functions, i.e. alertness or sustained attention. This would help to identify the relationship between the various vestibular cortical areas (Guldin & Grusser, 1998) and attentional functions organized in close vicinity to each other within the inferior and superior parietal lobe (Husain & Rorden, 2003) and the temporoparietal junction area (Friedrich, Egly, Rafal, & Beck, 1998).

9.3. Neuroplasticity and neurorehabilitation

Stroke is a major cause of chronic disability in all western societies. This problem is set to increase as the proportion of the elderly in these societies further increases. More effective treatments for stroke and its consequences are therefore urgently needed (Clarke, Black, Badley, Lawrence, & Williams, 1999). Here, tCDS may offer a valuable tool to study the online-effects, immediate aftereffects and the long-term-effects of single and repetitive applications (Schlaug et al., 2008). On their own many behavioural interventions for neuropsychological disorders (e.g. neglect therapy, cognitive training, physiotherapy) are not sufficient to promote full independence of the patient, such treatments might be enhanced by brain stimulation using the safe, portable, noninvasive and inexpensive technique of tDCS. As tDCS produces clear aftereffects after stimulation it may prolong the therapeutic effects of established behavioural treatments. To further augment the effects, tDCS could be combined with other *technical* (i.e. robotic arm training, grip force training, optokinetic neglect training) or behavioural treatments.

To conclude, tDCS holds promise as an important add-on-therapy in neurological and neuropsychological rehabilitation. But first it needs to be established that the effects observed in the above reviewed studies can be replicated and transformed into longer-lasting effects by using for example multi-session tDCS.

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