Hemispatial Neglect and Deficits of Verticality Perception After Stroke – Neuropsychological Results and Modulation via Galvanic Vestibular Stimulation

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Dipl.-Psych. Kathrin S. Utz

aus Tübingen

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Dekan:

Univ.-Prof. Dr. Jochen Kubiniok, Universität des Saarlandes

Berichterstatter:

Univ.-Prof. Dr. Georg Kerkhoff, Universität des Saarlandes

Univ.-Prof. Dr. Thomas Schenk, Friedrich-Alexander Universität Erlangen-Nürnberg

Univ.-Prof. Dr. Helmut Hildebrandt, Carl von Ossietzky Universität Oldenburg

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General Abstract

Hemispatial neglect is a multimodal syndrome that often follows unilateral right-brain damage. Patients with hemispatial neglect fail to notice or respond to sensory stimuli presented in the contralesional hemispace, which is not caused by primary motor or sensory deficits. Associated disorders often co-occurring with hemispatial neglect are deficits of verticality perception. Patients with those deficits show significant deviations in their subjective visual or haptic vertical away from the objective physical vertical when being asked to indicate whether a stepwise rotatable rod in the frontal plane is vertical, either by seeing the rod (visual modality) or by touching it when blindfolded (haptic modality).

Both, hemispatial neglect and disorders of verticality perception are very frequent and strongly related to substantial impairments in daily life. Thus, research on the subserving mechanisms and potential treatment methods is of high significance. Four studies were conducted, first addressing the potential benefits and risks of a new treatment method for patients with hemispatial neglect, and second investigating the multimodality of disorders of verticality perception and their occurrence in different spatial planes (frontal, sagittal).

Study 1 to 3 of the present doctoral thesis focus on a potential new treatment technique of hemispatial neglect and related disorders, the so-called galvanic vestibular stimulation (GVS). GVS uses weak direct current delivered via electrodes placed on the mastoids behind the ears. The direct current leads to polarization effects of the vestibular nerves and activations of multisensory vestibular brain areas, which are often lesioned in patients with hemispatial neglect and deficits of verticality perception.

In order to obtain a broad overview over the technique of GVS and the available evidence of its potential to modulate different neuropsychological phenomena, in Study 1 the scientific literature on GVS and the related technique of transcranial direct current stimulation (tDCS; electrodes are attached to the skull over the target cortical area) in the field of neuropsychology was reviewed. Both GVS and tDCS over the parietal cortex were proven to be able to modulate neglect and related disorders, with little evidence showing GVS-induced modulation of deficits of verticality perception.

Study 2 was concerned with the frequency and intensity of adverse effects during and after GVS in persons with stroke and healthy individuals, recorded via a questionnaire.

The results indicate only very few and slight adverse effects like mild itching and tingling underneath the electrodes during and after stimulation in both groups. Hence, GVS was shown to be a suitable and easily applicable technique for modulation with only minimal adverse effects.

In Study 3, the question was addressed whether GVS modulates a frequent neglect phenomenon, namely the rightward error in horizontal line bisection. GVS significantly decreased the rightward line bisection error during stimulation in right-brain-damaged patients with but not without neglect in contrast with sham stimulation. Right-cathodal GVS was more effective than left-cathodal GVS.

Finally, in Study 4 the subjective verticality judgments in two modalities (visual, haptic) and two spatial planes (frontal, sagittal) of right-brain-damaged patients with neglect, right-brain-damaged patients without neglect and age-matched healthy individuals were investigated using a novel testing device for all these tasks. We observed greater unsigned errors and significant perceptual tilts in the verticality judgments of right-brain-damaged patients with neglect in contrast to the other two groups. Tilts of the neglect patients were directed counterclockwise in the roll plane, and towards the observer in the sagittal plane for both modalities.

In summary, the studies presented in this work suggest that GVS is a promising treatment method which is able to modulate neglect phenomena and related disorders and is furthermore well-tolerated by persons with stroke and healthy individuals. The beneficial effects of GVS are most likely induced by activation of surviving remnants of the otherwise lesioned multimodal vestibular brain areas in neglect patients, thereby re-calibrating their disturbed spatial representations.

Furthermore the present thesis shows that deficits of verticality perception in neglect patients are multimodal and multispatial in nature. These impairments are presumably due to lesions of temporoparietal cortical regions involved in multisensory integration which leads to a disturbed representation of the vertical.

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Index of Publications

This doctoral thesis is based on four studies, of which one is published as a 'review' in an international peer-reviewed journal, one is submitted and two are published as 'original articles' in international peer-reviewed journals. I am the first author of all four articles. However, other authors also contributed to the work and are listed below. All articles are presented in the published form, except for changes in formatting (i.e. figure captions). References for all articles are provided at the end of this work.

Content	***has been published/submitted as***
Chapter II	Utz, K. S., Dimova, V., Oppenländer, K., & Kerkhoff, G. (2010). 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. *Neuropsychologia, 48*(10), 2789-2810.
Chapter III	Utz, K. S., Korluss, K., Schmidt, L., Rosenthal, A., Oppenländer, K., Keller, I., & Kerkhoff, G. (2011). Minor adverse effects of galvanic vestibular stimulation in persons with stroke and healthy individuals. Manuscript submitted for publication.
Chapter IV	Utz, K. S., Keller, I., Kardinal, M., & Kerkhoff, G. (2011). Galvanic vestibular stimulation reduces the pathological rightward line bisection error in neglect – a sham stimulation-controlled study. *Neuropsychologia, 49*(5), 1219-1225.
Chapter V	Utz, K. S., Keller, I., Artinger, F., Stumpf, O., Funk, J. & Kerkhoff, G. (2011). Multimodal and multispatial deficits of verticality perception in hemispatial neglect. *Neuroscience, 188,* 68-79.

Abbreviations

ANOVA	analysis of variance
BJLOT	Benton Judgment of Line Orientation Test
cf.	confer
cm	centimetre
cm^2	square centimetre
CVS	caloric vestibular stimulation
DC	direct current
DLPFC	dorsolateral prefrontal cortex
EEG	electroencephalography
e.g.	for example
EMG	electromyogram
ERPs	event-related potentials
fMRI	functional magnetic resonance imaging
GVS	galvanic vestibular stimulation
i.e.	that is
MEP	motor evoked potentials
M	mean
m	metre
M1	primary motor cortex
mA	milliAmpere
min	minute(s)
PET	positron emission tomography
PIVC	parieto-insular vestibular cortex
RBD+	right-brain-damaged patient(s) with neglect
RBD-	right-brain-damaged patient(s) without neglect
s	second(s)
SEM	standard error of the mean
SD	standard deviation
SEPs	somatosensory evoked potentials
SHV	subjective haptic vertical
SV	subjective vertical

SVH	subjective visual horizontal
SVV	subjective visual vertical
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation

Chapter I: General Introduction and Rationale

1.1 Hemispatial Neglect and Deficits of Verticality Perception: A General Introduction

Every year, three to five million individuals worldwide are affected by hemispatial neglect after stroke (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005). Hemispatial neglect (or [spatial] neglect or hemineglect)[1], often following unilateral brain damage, is commonly defined as a multimodal syndrome consisting in the failure to notice or respond to sensory stimuli in the contralesional hemispace, which is not simply the consequence of elementary motor or sensory deficits (Heilman, Valenstein, & Watson, 2000). Beyond the sensory domain, spatial representational deficits in imagination (Bartolomeo, D'Erme, & Gainotti, 1994; Bisiach, Capitani, Luzzatti, & Perani, 1981; Bisiach & Luzzatti, 1978; Rode, et al., 2010), or a decreased use of the contralesional extremities (Laplane & Degos, 1983; Vongiesen, et al., 1994) may occur. Characteristically, neglect patients show impairments in behavioural tests such as horizontal line bisection, where their markings of the lines' centre often deviate ipsilesionally (Schenkenberg, Bradford, & Ajax, 1980), or cancellation tasks, where they frequently omit targets on the contralesional side of the test sheet (M. L. Albert, 1973). In everyday life neglect patients may bump into door frames, eat only the food from the contralesional side of a plate, omit to shave, or to apply make-up on the contralesional side of their face (Mesulam, 1981). Various subtypes of neglect were described reflecting the great variety of clinical symptoms going far beyond the abovementioned phenomena (Buxbaum, 2006).

Besides neglect, deficits of spatial-perceptive orientation frequently follow unilateral brain damage, such as distortions in position estimation (Tartaglione, Benton, Cocito, Bino, & Favale, 1981; Tartaglione, Cocito, Bino, Pizio, & Favale, 1983), orientation discrimination (Taylor & Warrington, 1973; Warrington & James, 1967), judgments of oblique lines (A. Benton, Hannay, & Varney, 1975; De Renzi, Faglioni, & Scotti, 1971; Y. Kim, Morrow, Passafiume, & Boller, 1984) or judgment of the main spatial axes (M. Bender & Jung, 1948; Howard, 1982). With regard to deficits in the judgment of main spatial axes, patients show significant deviations in their subjective

[1] In the following the term "hemispatial neglect" and "(spatial) neglect" or "hemineglect" will be used synonymously.

visual vertical (SVV) or horizontal (SVH) larger than 2° from the veridical vertical or horizontal when being asked to indicate whether a stepwise rotatable rod is vertical or horizontal (M. Bender & Jung, 1948; Kerkhoff & Zoelch, 1998; Saj, Honore, Bernati, Coello, & Rousseaux, 2005). Such deviations were also observed in the subjective haptic vertical (SHV; Funk, Finke, Muller, Preger, & Kerkhoff, 2010; Kerkhoff, 1999; D. A. Perennou, et al., 2008) and the subjective postural vertical (SPV; D. A. Perennou, et al., 2008). In the first case patients are blindfolded and required to adjust a movable rod with one hand to the physical vertical and in the second case they have to signal when they feel upright during the rotation of a drum they are sitting in. Thus, deficits of verticality perception are apparent – like hemispatial neglect – in multiple modalities. Moreover, those deficits seem to manifest themselves not only in the frontal (roll) plane, but also in the sagittal (pitch) plane as shown for the SVV (Saj, Honore, Bernati, et al., 2005) and the SHV (Funk, Finke, Muller, Preger, et al., 2010). Here, patients showed a backward deviation in their judgments, that is, the upper end of the rod pointed towards the observer.

In the following, an overview of the neglect syndrome and deficits of verticality perception is given, addressing the neuroanatomy, explanatory models, frequency and prognosis, treatment methods, and the role of the vestibular system for both disorders. Finally this chapter gives an introduction to the aims of studies 1-4, presented subsequently in chapter II-V.

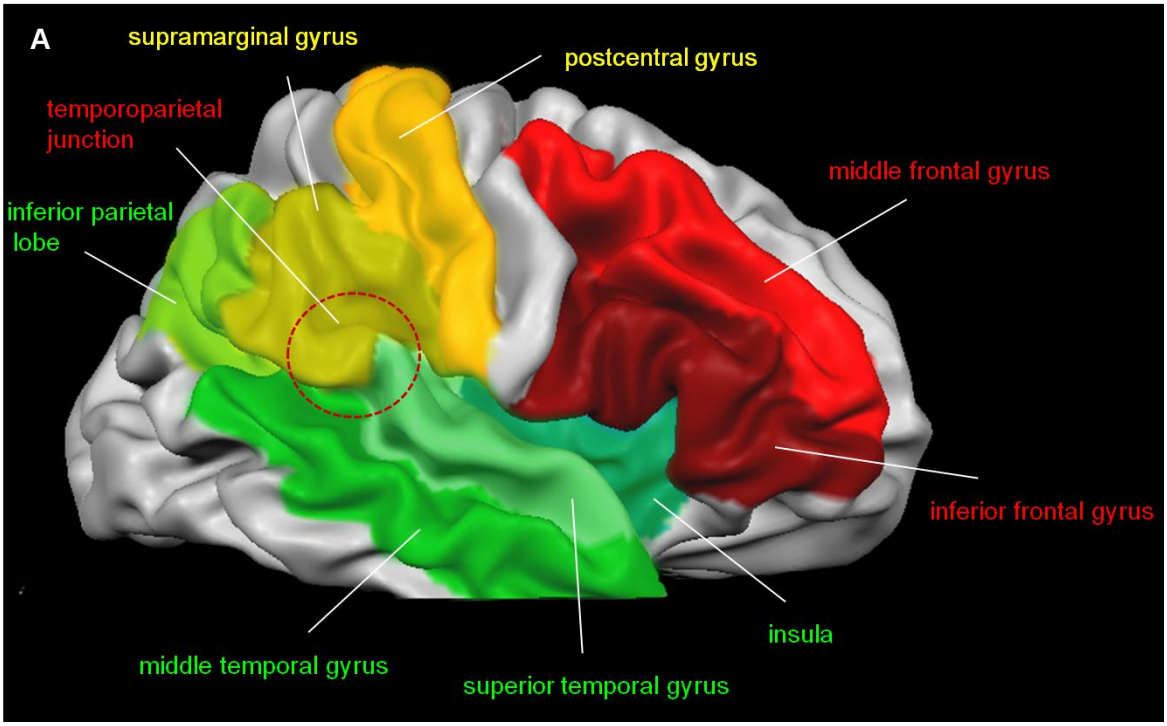
1.1.1 Underlying brain lesions

In most cases, neglect is caused by an infarction of the right middle cerebral artery (Vallar, Bottini, Rusconi, & Sterzi, 1993) leading to a wide range of lesions. Less frequent causes of neglect are tumours, traumatic injuries, degenerative diseases (Heilman, et al., 2000) or epileptic seizures (Prilipko, Seeck, Mermillod, & Pegna, 2006) of the same brain areas. Signs of neglect were observed in patients with lesions in the superior temporal cortex (Chechlacz, et al., 2010; Karnath, 2001; Karnath, Berger, Kuker, & Rorden, 2004; Karnath, Ferber, & Himmelbach, 2001), the inferior parietal cortex (Karnath, Rorden, & Ticini, 2009; Mort, et al., 2003; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010), middle temporal gyrus (Chechlacz, et al., 2010; Karnath, Rennig, Johannsen, & Rorden, 2011; Lee, et al., 2010; Verdon, et al., 2010), frontal lobes (Husain & Kennard, 1996; Husain, Shapiro, Martin, & Kennard, 1997; Verdon, et al., 2010), temporoparietal junction

(Chechlacz, et al., 2010) and the insula (Karnath, et al., 2004). Subcortical lesions of the basal ganglia (Karnath, et al., 2004; Karnath, Himmelbach, & Rorden, 2002; Karnath, et al., 2011; Karnath, Zopf, et al., 2005) and the thalamus (Karnath, et al., 2002) were also shown to cause neglect symptoms. In addition, lesions of white matter fibre tracts connecting cortical areas, such as the superior longitudinal fasciculus, the inferior and superior occipitofrontal fasciculus have been associated with neglect (Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007; Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomeo, 2008; Doricchi & Tomaiuolo, 2003; Karnath, et al., 2011; Karnath, et al., 2009; Verdon, et al., 2010). Currently, there is no consensus on the relative contribution of these brain areas to neglect. It seems that the functionally different deficits comprised in this multi-componential syndrome are caused by selective damage to specific lesion sites (Chechlacz, et al., 2010; Verdon, et al., 2010).

Comparatively little is known of the anatomical basis of deficits in verticality perception. Studies on the SVV in the roll plane showed that impairments of SVV judgments were caused by lesions of the supramarginal and postcentral gyrus (Von Cramon & Kerkhoff, 1993), the posterior insula (Barra, et al., 2010; Brandt, Dieterich, & Danek, 1994; Von Cramon & Kerkhoff, 1993), the superior temporal gyrus (Barra, et al., 2010; Darling, Pizzimenti, & Rizzo, 2003; Hegemann, Fitzek, Fitzek, & Fetter, 2004), the transverse temporal gyrus (Barra, et al., 2010; Brandt, et al., 1994), the thalamus (Dieterich & Brandt, 1993) and the brainstem (Friedman.G, 1970; Frisen, 2010). Parietal cortex lesions were shown to alter verticality perception in the visual, postural and haptic modality (D. A. Perennou, et al., 2008). Deficits in the SHV were associated with lesions in the middle temporal gyrus (Utz, Hildebrandt, Oppenländer, Keller, & Kerkhoff, 2011).

As can be seen from the above-reviewed studies, the lesion locations associated with neglect symptoms and those related to deficits in verticality perception are bordering or partially overlapping each other. Consequently, both clinical syndromes often co-occur (Kerkhoff, 1998; Yelnik, et al., 2002). Whether this co-occurrence of both disorders results from lesions of overlapping brain areas or whether SV deficits critically depend on the presence of neglect per se is debated (Johannsen, Fruhmann Berger, & Karnath, 2006; Kerkhoff, 1998; Yelnik, et al., 2002). Figure 1 illustrates cortical (A) and subcortical (B) brain areas typically lesioned in RBD patients with neglect and deficits of verticality perception, and lesions of white matter pathways in neglect patients (C).



B

See Figure 3.29 in *Biopsychologie* by J.P. J. Pinel 2007, München: Pearson Studium, p. 93.

C

See Figure 2a of "Left unilateral neglect as a disconnection syndrome", by P. Bartolomeo, M. Thiebaut de Schotten and F. Doricchi 2007, *Cerebral Cortex, 17*, 2479-2490.

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Figure 1 Typical cortical (A) and subcortical (B) lesion locations in patients with neglect and deficits of verticality perception, and lesions of white matter pathways in neglect patients (C). A, B: Red areas denote lesion locations of RBD patients with neglect, yellow areas refer to lesion locations in RBD patients with deficits of verticality perception and green areas denote to lesion locations associated with both disorders. Figure 1A was created with BrainVoyager Brain Tutor (Goebel, 2010) and modified. Figure 1B adapted from *Biopsychologie* by J.P. J. Pinel 2007, München: Pearson Studium. C: Lateral view of a normalized brain showing a 3-dimensional reconstruction of white matter pathways and the maximum overlap of neglect patients' subcortical lesions from 4 studies (pink, Doricchi and Tomaiuolo 2003; yellow, Mort et al. 2003; light blue, Karnath et al. 2004; green, Corbetta et al. 2005). From "Left unilateral neglect as a disconnection syndrome", by P. Bartolomeo, M. Thiebaut de Schotten and F. Doricchi 2007, *Cerebral Cortex, 17*, 2479-2490.

1.1.2 Theories of hemispatial neglect and deficits of verticality perception

Various theories on neglect exist, which can be assigned to about five main groups (for an overview see Kerkhoff, 2001). One of those groups comprises the so-called transformational theories, which are particularly important for the present work. These theories postulate an impairment of the transformation process in neglect, which turns peripheral sensory (visual, auditory, proprioceptive, vestibular) input into an egocentric frame of reference (referring to an object's position in relation to the viewer's body), important for correct motor output (Jeannerod & Biguer, 1989; Karnath, 1994). The transformation process presumably takes place in the parietal cortex (Andersen, 1995) and vestibular brain areas such as superior temporal cortex, insula and temporoparietal junction (Karnath & Dieterich, 2006), which are, as reviewed above, typical lesion sites in neglect patients. Vallar (1997) and Karnath (1997) postulated, that neglect is caused by an erroneous transformation process leading to a systematic ispilesional shift of the subjective straight ahead and poor exploration of the contralesional side of space. But, whereas Karnath (1997) suggested that this error results from a rotation of the midsagittal representation around the trunk midline, Vallar (1997) assumed a translation, that is, an ipsilesional shift in relation to the body midline.

In contrast to the multitude of theories for the explanation of the neglect syndrome, only few models of disturbed verticality perception exist. Most theories assume that the representation of the subjective vertical relies on the integration of visual, proprioceptive and vestibular input (Bronstein, 1999; Mittelstaedt, 1999) involving multimodal cortical regions (Brandt & Dieterich, 1999; Brandt, et al., 1994). Accordingly, Brandt et al. (1994) postulated a graviceptive pathway proceeding from the brainstem to the thalamus and from there to the vestibular cortex. As outlined above, the lesion sites associated with perturbed verticality perception are typically located along this graviceptive pathway. Thus, impaired verticality perception seems to result from asymmetrical sensory integration following brain lesions along the graviceptive pathway. The notion, that the disruption of any subcortical or cortical brain region along the graviceptive pathway rather than damage to one particular brain area causes impairments in verticality perception, is underlined by studies showing that not the lesion location but the lesion size influenced the occurrence and severity of the SVV (Barra, et al., 2010) and SPV (D. A. Perennou, et al., 2008) tilts.

To sum up, both neglect and disturbed verticality perception critically depend on the integration of sensory input from different sources with the multimodal vestibular system playing a crucial role in the processing of this information. Thus, the following section gives an overview of the vestibular system.

1.1.3 The vestibular system

The vestibular system is essential for the sensation of the position and movement of our body in space. For this purpose it acts jointly with the visual, auditory and proprioceptive system via integration of redundant information of the surrounding space (Brandt & Dieterich, 1999).

The two labyrinths in the inner ears comprise the end organs of the vestibular system: two otoliths (utricle and saccule), which assess linear accelerations caused by body motion or gravity and three semicircular canals, detecting angular accelerations due to body or head rotation. The semicircular canals are aligned approximately orthogonally to one another, thus permitting the detection of rotation in every spatial plane. The otholiths are aligned nearly orthogonally to one another, too, whereas the macula utriculi respond to horizontal and the macula saccule to vertical directed gravitoinertial force (M. E. Goldberg & Hudspeth, 2004). Mechanical stimuli are transduced into receptor potentials by the labyrinths' hair cells, where different discharge patterns code the direction and amplitude of accelerations (Fernandez & Goldberg, 1976; J. M. Goldberg & Fernandez, 1971).

Efferents and afferents are comprised in the vestibular nerve and project to the vestibular nuclei in the brainstem, which also receive afferent input from the visual and proprioceptive system (Goldstein, 2002). From there vestibular pathways proceed to nuclei in the cerebellum, spinal tract and brainstem subserving ocular motor, postural and fine motor functions essential for keeping one's balance. Further anatomical connections project to a thalamo-cortical network contributing to multisensory perception (Zwergal, Strupp, Brandt, & Buttner-Ennever, 2009).

There is no primary vestibular cortex, but various multisensory areas responding not only to vestibular input but also to proprioceptive and visual stimuli (Brandt & Dieterich, 1999). These areas are primarily located around the posterior parietal cortex, the somatosensory cortex, medial and lateral frontal cortices, the temporoparietal junction and the anterior and posterior insula (for a review see Lopez & Blanke, 2011).

In the monkey brain, the parieto-insular vestibular cortex (PIVC) on the posterior end of the insula is assumed to serve as the core integration area for all the other vestibular regions, because it is connected with all of them as well as with the vestibular nuclei in the brainstem (Grusser, Pause, & Schreiter, 1990a, 1990b; Guldin, Akbarian, & Grusser, 1992; Guldin & Grusser, 1998).

See Figures 3B and 8A of "The thalamocortical vestibular system in animals and humans", by C. Lopez and O. Blanke, 2011, *Brain Research Reviews, 67*, 119-146.

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Figure 2 Anatomy of the human vestibular cortex. (A) Vestibular areas described in epileptic patients. Green and purple open circles represent the location of epileptogenic lesions responsible for vestibular sensations. Filled symbols represent the site at which focal electrical stimulation of the cortex evoked vestibular illusions in awake epileptic patients. The numbers refer to the Brodmann areas (modified after Duvernoy, 1999). (B) Vestibular areas in humans revealed by neuroimaging during caloric (red symbols) and galvanic (blue symbols) vestibular stimulation, as well as during short auditory stimulation (yellow symbols). To summarize, right and left cerebral activations are reported on a lateral view of the right hemisphere (modified after Duvernoy, 1999). The supposed homologous vestibular areas reported in animals are indicated in bold letters (FEF: frontal eye fields; MIP: medial intraparietal area, MST: medial superior temporal area, PIVC: parieto-insular vestibular cortex, VIP: ventral intraparietal area,). From "The thalamocortical vestibular system in animals and humans", by C. Lopez and O. Blanke, 2011, *Brain Research Reviews, 67*, 119-146.

The posterior insula and the temporoparietal junction are believed to be the human homologue of the PIVC according to neuroimaging studies in healthy individuals (Bense, Stephan, Yousry, Brandt, & Dieterich, 2001; Bottini, et al., 1994; Bucher, et al., 1998) and clinical data (Barra, et al., 2010; Boiten, Wilmink, & Kingma, 2003; Brandt, et al., 1994; Nicita, et al., 2010). However, there is also evidence indicating that the PIVC might be located in the parietal operculum (Eickhoff, Weiss, Amunts, Fink, & Zilles, 2006) or in the temporo-peri-sylvian vestibular cortex (Kahane, Hoffmann, Minotti, & Berthoz, 2003). Figure 2 illustrates the anatomical regions of the human vestibular cortex found via neuroimaging and clinical studies in epileptic patients receiving electrical cortical stimulation.

1.1.4 Frequency and prognosis of neglect and deficits of verticality perception

The reported frequency of neglect following stroke depends on the tests used to assess the disorder as well as on the time of measurement post lesion. In acute stroke (within seven days post lesion) 43-82 % of right-brain-damaged patients and 20-65 % of left-brain-damaged patients were found to suffer from neglect (Fullerton, McSherry, & Stout, 1986; Ringman, Saver, Woolson, Clarke, & Adams, 2004; S. P. Stone, Halligan, & Greenwood, 1993; S. P. Stone, et al., 1991). About two months post stroke, Halligan, Marshall and Wade (1989) still found signs of neglect in 48 % of right-brain-damaged and in 15 % of left-brain-damaged patients, whereas Ringman, et al. (2004) reported neglect in 17 % of RBD and 5 % of left-brain-damaged patients three months post stroke. Despite the differences in the reported neglect frequencies it becomes apparent from all studies that neglect occurs more often in right-brain-damaged patients than in left-brain-damaged patients. Furthermore, neglect is more severe and longer lasting after right brain damage compared with left brain damage (S. P. Stone, et al., 1991). This asymmetry has also been reported for deficits in the SVV by Bonan, Leman, Legargasson, Guichard, and Yelnik (2006) who observed a better recovery in left-brain-damaged patients compared with right-brain-damaged patients. At six months post lesion, 12.5 % of the initially 47 % impaired left-brain-damaged patients still displayed perceptual tilts compared with 50 % of the initially affected 61 % of the right-brain-damaged patients. Perennou, et al. (2008) investigated the SVV, SHV and SPV in 80 patients with hemispheric stroke and found in 52 % perturbations in one of the three modalities and in 22 % transmodal tilts, thus in all three modalities. 94 % of the patients with transmodal tilt were right-brain-damaged. Furthermore SPV tilts were more pronounced in right-brain-damaged compared to left-brain-damaged patients, which was not observed for SVV and SHV tilts.

In a large portion of patients spontaneous recovery of neglect occurs (Campbell & Oxbury, 1976), but remains chronic in one third (approximately one year post lesion; Karnath, et al., 2011). Beyond the mere lesion side (left vs. right hemisphere) also the lesioned brain structure predicts recovery from neglect. Chronic neglect was shown to be associated with lesions of the superior and middle temporal gyri, basal ganglia and the inferior occipitofrontal fasciculus (Karnath, et al., 2011). Rengachary, He, Shulman, and Corbetta (2011) found in a longitudinal study of recovery that patients with lesion in the ventral frontal cortex had the most severe neglect symptoms indicating a disturbed

"communication" between frontal and parietal brain areas (the so-called "fronto-parietal attentional network"). Furthermore, they showed that lateralized spatial impairments were more pronounced, and that recovery was more variable in the perceptual and attentional than in the motor domain. Additionally, recovery was shown to be more likely for smaller lesions (Hier, Mondlock, & Caplan, 1983; Levine, Warach, Benowitz, & Calvanio, 1986) and more complete in patients without cortical atrophy (Levine, et al., 1986). In spite of recovery in the majority of neglect patients, the presence of neglect after brain damage highly predicts long-lasting sensory-motor and cognitive impairments as well as a decreased functioning in activities of daily living (Katz, Hartman-Maeir, Ring, & Soroker, 1999).

Little is known regarding the recovery from deficits of verticality perception after stroke. Besides the abovementioned poorer recovery in right-brain-damaged patients, SVV tilts predict unfavourable balance recovery after stroke (Bonan, et al., 2007), as well as impairments in ambulation capacity in the presence of a hemiparesis/hemiplegia (Bruell & Peszczynski, 1958; Bruell, Peszczynski, & Volk, 1957).

1.1.5 Intervention through sensory stimulation and brain stimulation

Given the high frequency of neglect and perturbations of verticality perception after brain lesions and the persisting impairments in about one third of the patients, effective treatment methods are of major importance. Therefore, a great variety of therapeutic techniques for neglect have been developed over the previous 60 years (for reviews see Chokron, Dupierrix, Tabert, & Bartolomeo, 2007; Kerkhoff, 2003; Luaute, Halligan, Rode, Jacquin-Courtois, & Boisson, 2006).

One promising approach for treatment of spatial neglect is sensory stimulation (for an overview see Kerkhoff, 2003). Techniques like caloric vestibular stimulation (CVS; irrigation of the ears with warm or cold water; Rode, Perenin, Honore, & Boisson, 1998), optokinetic stimulation (stimulation by visual stimuli moving to the contralesional side; Kerkhoff, Keller, Ritter, & Marquardt, 2006; Pizzamiglio, et al., 2004), neck muscle vibration (vibration of contralesional neck muscles; Schindler & Kerkhoff, 2004; Schindler, Kerkhoff, Karnath, Keller, & Goldenberg, 2002), transcutaneous electrical nerve stimulation (stimulation of nerves by electric current; Vallar, et al., 1995), limb activation (active movements of the contralesional arm in the contralesional space;

Robertson & North, 1993) and prism adaptation (optical shifting via prismatic goggles; Rossetti, et al., 1998) were shown to modulate various neglect signs, at least transiently.

The theoretical basis of these techniques are the transformational neglect theories (see 1.1.2), postulating a shift of the egocentric reference frame which is based on the integration of visual, vestibular and proprioceptive information. However, an alternative assumption with respect to the mechanism of action is also discussed, suggesting that the modulation of neglect signs by those methods is induced by a reorientation of attention towards the contralesional left side (Gainotti, 1993, 1996; Kerkhoff, et al., 2006).

Beyond the transient effects of those techniques on neglect phenomena, longer-lasting improvements have been shown for repetitive optokinetic stimulation (Kerkhoff, et al., 2006), neck muscle vibration (Schindler, et al., 2002) and prism adaptation (Frassinetti, Angeli, Meneghello, Avanzi, & Ladavas, 2002; Vangkilde & Habekost, 2010). Furthermore, the combination of different techniques such as visual scanning training and optokinetic stimulation (Schroder, Wist, & Homberg, 2008) or visual exploration training and neck muscle vibration (Schindler, et al., 2002) have turned out to be particularly effective.

Optokinetic stimulation (via visual input), neck muscle vibration (via proprioceptive input) and caloric vestibular stimulation (via vestibular input) all activate the above described cortico-subcortical vestibular network involving temporal, parietal and insular cortices, the thalamus and basal ganglia (Bottini, et al., 2001; Bottini, et al., 1994; Dieterich, Bucher, Seelos, & Brandt, 1998; Suzuki, et al., 2001). In addition, every stimulation method induces specific cortical and subcortical activations beyond those of the vestibular network (cf. Chokron, et al., 2007). Because this system operates in a multisensory way, stimulation techniques targeting it, seem to be predestined to alleviate the multimodal deficits of the neglect syndrome as well as the multimodal deficits of verticality perception. While long-term effects of repetitive optokinetic stimulation (Kerkhoff, et al., 2006) and repetitive neck muscle vibration (Schindler, et al., 2002) on neglect phenomena have been shown, no study exists, using repetitive CVS. The reasons for this lack of evidence are probably the potential side effects associated with CVS such as vertigo, nystagmus and nausea (Bottini, et al., 2001), and habituation processes (Henriksson, Kohut, & Fernandez, 1961; Rode, et al., 1998) of the vestibular system during repetitive stimulation of this type, whereas habituation in GVS only occurs after the first stimulation and remains stable thereafter (Balter, et al., 2004).

Recently, non-invasive brain stimulation techniques have also been shown to ameliorate neglect phenomena – at least transiently – such as repetitive transcranial magnetic stimulation (rTMS) over the right parietal cortex which even induced longer-lasting improvements (Brighina, et al., 2003; Oliveri, et al., 2001; Shindo, et al., 2006). This technique uses a magnetic field to induce weak electric currents modulating the excitability of the underlying brain tissue. A related technique is transcranial direct current stimulation (tDCS), which uses weak direct current to alter cortical excitability. More specifically, electrodes of different polarity, connected with a portable direct current stimulator, are placed on the scalp over the targeted cortical area (Nitsche & Paulus, 2001). In a study using tDCS over the posterior parietal cortex in neglect patients, improved target detection of the patients in the contralateral hemifield during stimulation has been observed (Sparing, et al., 2009). In contrast to (r)TMS, which may induce headache, local pain and in the worst case seizures (Rossi, Hallett, Rossini, & Pascual-Leone, 2009; Wassermann, 1998), tDCS is considered to be relatively safe and does not induce severe adverse effects (Iyer, et al., 2005; Nitsche, Liebetanz, et al., 2003; Poreisz, Boros, Antal, & Paulus, 2007). Consequently, it might be the more suitable brain stimulation technique for repetitive stimulation. Beside the unpleasant possible side effects of (r)TMS, another disadvantage of this technique concerns its suitability for research of its therapeutic effects, namely that sham (placebo) stimulation is difficult to realize, because real (r)TMS produces specific noise, tap sensations, and sometimes muscle twitches. Here, tDCS might be the better choice, because sham stimulation is easier to realize with tDCS in contrast to (r)TMS (Gandiga, Hummel, & Cohen, 2006).

If vestibular brain areas are intended to be stimulated via direct current, galvanic vestibular stimulation (GVS) can be used. Instead of placing the electrodes over the scalp as for tDCS, they are placed on the mastoids behind both ears (Been, Ngo, Miller, & Fitzgerald, 2007). The direct current leads to polarization effects of the vestibular nerves underneath the mastoids (J. M. Goldberg, Smith, & Fernandez, 1984) and activation of multisensory vestibular brain areas (see Figure 2B), similar to CVS (Bense, et al., 2001; Bucher, et al., 1998). GVS has been shown to reduce neglect signs transiently (Rorsman, Magnusson, & Johansson, 1999), without producing those adverse effects typically associated with CVS (Rorsman, et al., 1999; Wilkinson, Zubko, & Sakel, 2009). Thus, GVS seems to be, like tDCS, especially eligible for repetitive stimulation in the context of treatment.

Little is known so far regarding the modulation or even treatment of deficits of verticality perception after stroke. Saj, Honore, and Rousseaux (2006) showed that GVS decreased the counterclockwise tilts of the SVV in right-brain-damaged patients. Furthermore, a study using neck muscle vibration has proven to modulate SVV settings in the frontal plane in healthy subjects (McKenna, Peng, & Zee, 2004) and might also prove effective in order to reduce SV tilts in stroke patients.

1.2 Rationale of the Present Investigations

In the light of the high frequency of hemispatial neglect and disorders of verticality perception and the considerable impairments in daily life associated with them, especially in the face of an increasingly aging society with a steadily increasing incidence of stroke victims, the investigation of the mechanisms and potential treatment techniques for these disorders is of high scientific and practical relevance.

A general objective of the present thesis was therefore to investigate the potential benefits and risks of a new treatment method for patients with hemispatial neglect, focussing on a review of the existing literature, safety aspects and its capacity to reduce neglect signs in stroke patients.

A further main aim of this thesis was to shed more light on the disturbances of verticality perception, a phenomenon often co-occurring with neglect, but which has not been investigated as thoroughly. Particularly, the multimodality of this disorder and the pattern of impairments in different spatial planes were of interest here.

This thesis comprises four studies, which were conducted to accomplish those purposes and which I will briefly introduce in the following. Figure 3 graphically illustrates which aspects are addressed by the different studies.

As outlined above, GVS and tDCS seem to carry the potential of modulating neglect phenomena without adverse effects associated with the related stimulation techniques CVS and (r)TMS (Brighina, et al., 2003; Oliveri, et al., 2001; Rorsman, et al., 1999; Shindo, et al., 2006). Thus, these methods might be predestined for repetitive stimulation to achieve long-lasting improvements in neglect patients. The aim of the first investigation was therefore to review a large part of the existing literature on tDCS and GVS in the field of neuropsychology. In order to get a comprehensive overview of the techniques, literature on their origin, the stimulation procedures, the mechanisms of action,

their safety and empirical evidence of their effects on a great variety of neuropsychological functions in healthy individuals as well as patients with different psychiatric and neuropsychological disorders was reviewed.

Due to previous positive experiences with GVS in neglect patients in pilot experiments of the Clinical Neuropsychology Department, Saarland University, and the role of the vestibular system for both hemispatial neglect and deficits of verticality perception, this method was chosen instead of parietal tDCS to further investigate its potential to modulate neglect. However, when studying the effects of a new method in both patients and healthy individuals, it is of great importance to evaluate the potential risks of this technique, too. Several studies exist on the safety and tolerance of tDCS, suggesting that this method is safe if certain standards are kept and associated with only minor adverse effects such as slight headache or mild skin itching underneath the electrodes (Iyer, et al., 2005; Nitsche, Liebetanz, et al., 2003; Nitsche, Niehaus, et al., 2004; Nitsche & Paulus, 2001; Poreisz, et al., 2007). However, little is known on potential adverse effects of GVS. Thus, the objective of Study 2 was to assess the frequency and intensity of adverse effects during and after GVS with two different current strengths and different stimulation conditions in healthy individuals and persons with stroke with and without neglect.

Finally, in Study 3 the capacity of GVS to modulate a phenomenon often manifest in neglect patients, namely the rightward deviation in horizontal line bisection was investigated more detailed. In this task one or several horizontal lines are presented on a sheet of paper and patients have to mark the centre of each line. Typically, right-brain-damaged patients with left-sided neglect mark the lines too far to the ipsilesional side (the side of their brain lesion; Halligan, Manning, & Marshall, 1990). This task is, among others, frequently used for the assessment of visual neglect and performance has been shown to be influenced by sensory stimulation techniques (Pizzamiglio, Frasca, Guariglia, Incoccia, & Antonucci, 1990; Rossetti, et al., 1998; Schindler & Kerkhoff, 2004). To answer the question, whether GVS influences this deficit in neglect, in Study 3 right-brain-damaged patients with visual neglect and right-brain-damaged patients without visual neglect were investigated with a modified horizontal line bisection task *while* receiving GVS in three different stimulation conditions.

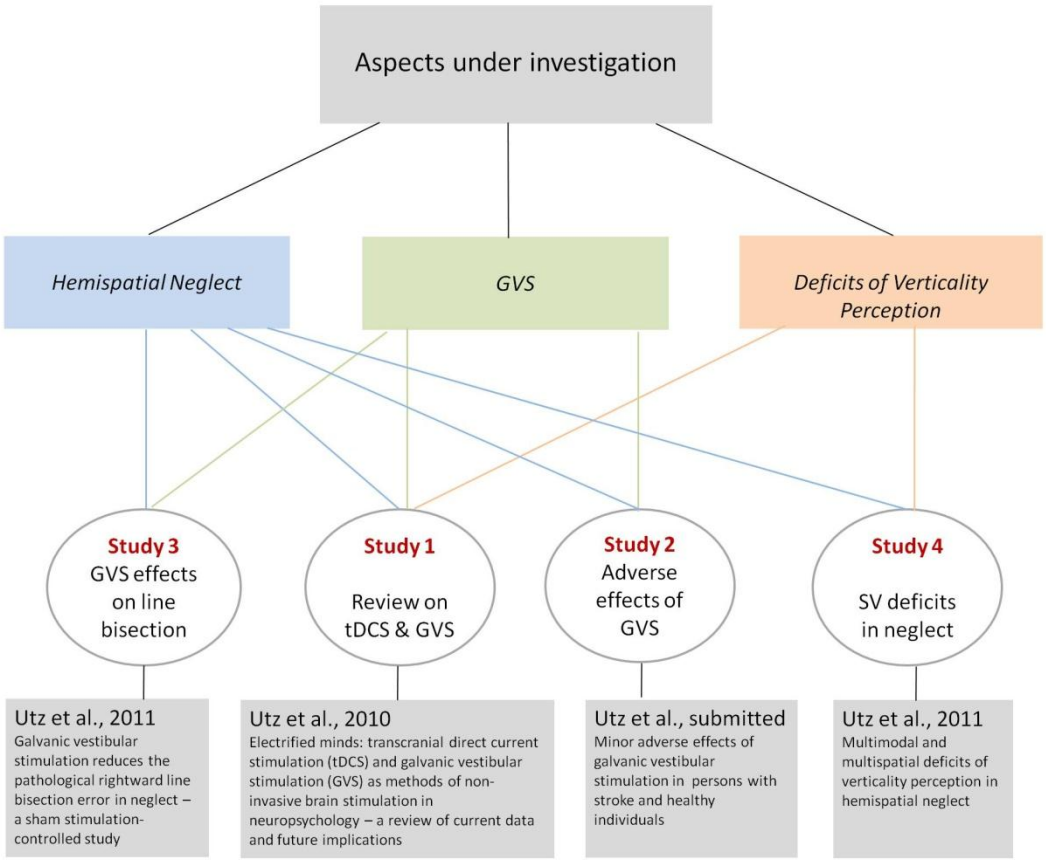

Figure 3 Graphical overview over the aspects under investigation of the present studies/articles. GVS: galvanic vestibular stimulation; SV: subjective vertical; tDCS: transcranial direct current stimulation.

Study 4 addresses the second main aim of the present thesis, namely to gain deeper insights into the disturbances of verticality perception in multiple modalities and different spatial planes, as observed after stroke. In this investigation, right-brain-damaged patients with neglect, right-brain-damaged patients without neglect and age-matched healthy individuals had to perform a SV task in two modalities (visual and haptic) and two spatial planes (frontal and sagittal) using the same testing device for all these tasks. This was the first study on the SV combining different modalities and different spatial planes in one sample of patients and matched healthy individuals. Thus, direct comparisons between modalities and spatial planes as well as the analysis of their intercorrelations were possible.

Studies 1 to 4 are presented in the subsequent chapters II to V of this thesis, followed by a general discussion of the studies in chapter VI.

Chapter II: Study 1

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

Utz, K. S., Dimova, V., Oppenländer, K., & Kerkhoff, G. (2010). Neuropsychologia, 48(10), 2789-2810.

doi: 10.1016/j.neuropsychologia.2010.06.002

Chapter III: Study 2

Minor Adverse Effects of Galvanic Vestibular Stimulation in Persons with Stroke and Healthy Individuals

Utz, K. S., Korluss, K., Schmidt, L., Rosenthal, A., Oppenländer, K., Keller, I., & Kerkhoff, G. (2011). Manuscript submitted for publication.

doi: 10.3109/02699052.2011.607789

Chapter IV: Study 3

Galvanic Vestibular Stimulation Reduces the Pathological Rightward Line Bisection Error in Neglect – A Sham Stimulation-Controlled Study

Utz, K. S., Keller, I., Kardinal, M., & Kerkhoff, G. (2011). Neuropsychologia, 49(5), 1219-1225.

doi: 10.1016/j.neuropsychologia.2011.02.046

Chapter V: Study 4

Multimodal and Multispatial Deficits of Verticality Perception in Hemispatial Neglect

Utz, K. S., Keller, I., Artinger, F., Stumpf, O., Funk, J. & Kerkhoff, G.(2011).

Neuroscience, 188, 68-79.

doi: 10.1016/j.neuroscience.2011.04.068

Chapter VI: General Discussion

The general aims of the present thesis were to study a new stimulation technique for modulating neglect symptoms and to broaden our knowledge about the multimodal and multispatial characteristics of deficits in verticality perception. Four studies were conducted and presented in this thesis to accomplish the mentioned purposes. After a short summary of the studies, I will discuss the results in the light of current literature and address their implications for the clinical practice and neuropsychological research. Then I will discuss prospects for future research and end with a general conclusion.

6.1 Summary

With regard to the investigation of a new stimulation technique for the modulation of hemispatial neglect, Study 1, 2 and 3 were performed. In order to get a broad overview of tDCS and GVS, literature on both techniques in the domain of neuropsychology was reviewed in Study 1. The literature review revealed that both methods are easily applicable, modulate a broad range of neuropsychological functions and induce long-lasting neuroplastic changes making the two techniques attractive for neuropsychological research as well as for clinical neurorehabilitation. Particularly the effects on neglect are of great interest for this work. Here, both tDCS of the parietal cortex and GVS were proven to effectively modulate visual neglect (e.g. Rorsman, et al., 1999; Sparing, et al., 2009; D. B. Stone & Tesche, 2009). Furthermore, GVS was also shown to modulate neglect-related disorders such as tactile extinction (Kerkhoff, et al., 2011) and deficits of verticality perception (i.e. Saj, et al., 2006; Oppenländer et al., unpublished results).

In a second step, the tolerability of GVS, that is the occurrence and intensity of adverse effects during and after the stimulation in healthy individuals and persons with stroke was investigated using a self-report questionnaire (Study 2). Only very few and slight adverse effects like mild itching and tingling underneath the electrodes during and after stimulation were reported. No differences between healthy participants and persons with stroke (with and without hemispatial neglect) were evident. Adverse effects were more frequently observed with GVS of 1.5 mA as compared to subsensory GVS and subject blinding of the stimulation condition (i.e. sham vs. real stimulation) was shown to be more easily realisable with subsensory GVS. In sum, Study 2 showed that GVS is a well

tolerated and safe technique in healthy individuals and persons with stroke when safety guidelines are adhered to. Therefore GVS is suitable for repetitive stimulation (i.e for treatment).

Finally, in a third step, the question was addressed (Study 3) whether GVS modulates the rightward line bisection error in neglect. Right-brain-damaged patients with visual neglect and right-brain-damaged patients without visual neglect were investigated with a modified horizontal line bisection task while receiving GVS in three different stimulation conditions, including a sham-stimulation condition. Left- and right-cathodal GVS significantly decreased the rightward line bisection error in right-brain-damaged patients with but not without neglect in contrast with sham stimulation. Right-cathodal GVS provoked a stronger effect. It was proposed, that the ameliorating effect of GVS was caused by an activation of preserved structures of the otherwise lesioned right posterior parietal cortex.

With regard to the investigation of deficits of verticality perception, in Study 4 verticality judgments in two modalities (visual, haptic) and two spatial planes (roll, pitch) of right-brain-damaged patients with neglect, right-brain-damaged patients without neglect and age-matched healthy individuals were investigated using the same, novel testing device for all these tasks. Participants had to adjust a rod that was either rotatable in the roll or in the pitch plane, to the veridical vertical with open eyes (visual modality) or blindfolded (haptic modality). We observed greater unsigned errors (mean error of deviation irrespective of its direction) and significant tilts in the verticality judgments of right-brain-damaged patients with neglect, both in the haptic and visual modality, and both in the role and pitch plane as compared with right-brain-damaged patients without neglect and healthy individuals. We could provide clear evidence for the multimodal as well as multispatial nature of the deficits of verticality perception in hemispatial neglect. Furthermore, the use of the same testing device for all tasks allowed for the first time unbiased comparisons between verticality judgments in different modalities and spatial planes. Here, positive correlations between verticality judgments in different spatial planes and different modalities were found, suggesting a multimodal and multispatial disorder of verticality perception in patients with neglect.

6.2 GVS as a Means for Modulating Neglect and Related Disorders

Studies 1, 2 and 3 suggest that GVS is a promising treatment method which has the capacity to modulate neglect phenomena and related disorders and is moreover well-tolerated by both persons with stroke and healthy individuals.

More specifically, the reviewed experiments in Study 1 and the results of Study 3 show that GVS ameliorates various multimodal deficits in right-brain-damaged patients, namely the rightward line bisection error in neglect (Study 3; Oppenländer et al., unpublished results; see Study 1), SVV and SHV tilts (Saj, et al., 2006; Oppenländer et al., unpublished results, see Study 1), omissions in cancellation tasks (Rorsman, et al., 1999; Oppenländer et al., unpublished results, see Study 1) visuoconstructive deficits (Wilkinson, et al., 2005) and tactile extinction (Kerkhoff, et al., 2011). Together, these results are promising regarding a future therapeutic application of GVS for the treatment of neglect and related disorders. An important and valuable feature of GVS is that it induces multimodal effects, thus carrying the potential to simultaneously ameliorate deficits in different modalities which are comprised in the multicomponential syndrome of hemispatial neglect. Furthermore, GVS not only acts on neglect phenomena, but also influences related disorders like tactile extinction (Kerkhoff, et al., 2011) and deficits of verticality perception (Saj, et al., 2006;Oppenländer et al., unpublished results). Consequently, because of the overall effects of GVS, treatment with this method should lead to better recovery in comparison to pure behavioural techniques that act on deficits in one modality (e.g. visual search training).

Beyond the reviewed beneficial effects of GVS in the respective patients, this technique provides many advantages enhancing its applicability in neurorehabilitation: It is easy to administer and cheaper compared to TMS for example. Furthermore the relative short duration per session (20 min GVS at a maximum in accordance with safety standards) contributes to the economical advantages of GVS and furthermore prevents patients from signs of fatigue. Probably even shorter durations might be effective as indicated by the result of Study 3, whereby 40 s of current flow during sham stimulation elicited the same behavioural effect as 20 min left-cathodal GVS. Another valuable aspect of GVS is that it can easily be used as an add-on treatment in conjunction with other treatment methods for neglect such as optokinetic stimulation, exploration, or attention training.

Interestingly, it has already been shown that such a combination of different treatment methods is particularly effective (visual scanning training *plus* optokinetic stimulation; Schroder, et al., 2008 or visual exploration training *plus* neck muscle vibration; Schindler, et al., 2002). Finally, the lack of serious adverse effects, as shown in Study 2, increases the patients' compliance and speaks for the applicability of GVS for longer stimulation durations and repetitive stimulation, which cannot be realized with the related technique caloric vestibular stimulation (CVS). This method consists of the irrigation of the ears with warm or cold water and was shown to transiently reduce neglect signs (Rode, et al., 1998). Repetitive stimulation is not practicable with CVS because it is associated with unpleasant adverse effects such as vertigo, nystagmus and nausea (Bottini, et al., 2001).

The exact mechanisms underlying the effects of GVS on hemispatial neglect and related disorders have not been fully elucidated yet. Based on animal studies (J. M. Goldberg, et al., 1984) and imaging studies in healthy individuals showing cortical activations in multimodal vestibular brain areas during GVS (Bense, et al., 2001; Bucher, et al., 1998; Fink, et al., 2003), it can be assumed that the beneficial effects of GVS are most likely induced by polarization effects of the vestibular nerves leading to activation of intact parts of the otherwise lesioned multimodal vestibular brain areas in neglect patients thereby altering their disturbed spatial orientation, perception and representations. Here, GVS seems to act on different aspects of spatial representations like egocentric (cancellation tasks), allocentric (line bisection tasks), and gravitational (SVV and SHV) representations.

In line with this notion for the explanation of the effects of GVS, the results of Study 3 show a decreased rightward line bisection error in neglect patients during GVS. The neglect patients had lesions in the posterior parietal cortex, a cortical region known to be involved in horizontal line bisection (Fink, et al., 2000) and was shown to be activated in healthy individuals during performance of a horizontal line bisection task while receiving GVS (Fink, et al., 2003), along with ventral premotor cortex activations. The observed effects of GVS in Study 3 might be based on the activation of anatomically intact parts of the otherwise lesioned parietal cortex or the activation of the frontal cortex compensating for the parietal lesion. Notably, frontal cortex was structurally intact in all but one neglect patient of Study 3.

Whether GVS in the lesioned brain activates the postulated vestibular brain areas as found in healthy individuals is to date unclear. Due to a lack of structural brain images in some of the studied patients (Study 3), as well as in all other available studies on GVS (Kerkhoff, et al., 2011; Rorsman, et al., 1999; Saj, et al., 2006), it can only be assumed that the ameliorating effects of GVS are caused by activations of preserved structures of the otherwise lesioned vestibular brain areas. A PET study supports the notion that recovery from neglect is mediated by spared brain areas in the right hemisphere (Pizzamiglio, et al., 1998).

Apart from lesion locations the effects of polarity of GVS is a relevant issue. In Study 3 left- *and* right-cathodal GVS both had an ameliorating effect on the rightward line bisection error in neglect patients, whereas right-cathodal GVS induced the stronger effects. In contrast, a previous study by Oppenländer et al. (unpublished results, see Study 1), observed a reduction of the rightward line bisection error in neglect only for left-cathodal GVS (but with another task version: patients had to bisect 3 lines; Fels & Geissner, 1996, whereas in Study 3 patients had to bisect 17 lines; Schenkenberg, et al., 1980). A probable reason for those differential effects could be the different current strengths administered in the two studies. In the study carried out by Oppenländer et al., patients received subsensory GVS (0.7mA on average), whereas in the present Study 3 GVS with 1.5 mA was used. In this regard, a study of Zink, Bucher, Weiss, Brandt, and Dieterich, (1998) reported differential effects of GVS on eye movements in healthy subjects depending on the applied current strength. With lower current strength (1-3mA) otoliths were activated by GVS, while both otoliths and semicircular canals responded to GVS leading to differential eye movements with intensities above 3mA.

Moreover, we cannot exclude the possibility that the patient samples of the two studies had slightly different lesion locations, leading to different activation patterns and consequently to somewhat different behavioural effects. In this respect, the study of Fink et al. (2003) is relevant, showing asymmetric patterns of activation during left- and right-cathodal GVS in healthy individuals. Whereas left-anodal/right-cathodal GVS unilaterally activated right-hemispheric vestibular brain areas, right-anodal/left-cathodal GVS led to bilateral cortical activation (Fink, et al., 2003). Referring to the differential results of Oppenländer et al. and Study 3 one could speculate that patients in the Oppenländer et al. study might have had larger lesions in the right hemisphere. As a consequence the left hemisphere could compensate for the deficits during left-cathodal GVS, because this type

of stimulation leads to *bilateral* cortical activations, whereas right-cathodal GVS *unilaterally* activates right-hemispheric vestibular areas (Fink, et al., 2003) which might be lesioned to a larger extent in the Oppenländer et al. sample. In contrast, the patients in Study 3 might have had smaller right-hemispheric lesions and therefore both left-cathodal GVS and right-cathodal GVS were effective. The activated remnants of the right posterior parietal cortex during right-cathodal GVS could have compensated for the deficits caused by the otherwise lesioned parts of this brain area (see above). Because the right posterior parietal cortex is especially involved in line bisection (Fink, et al., 2000), right-cathodal stimulation could have had a stronger effect in this sample compared to the bilateral, but relatively weaker right-hemispheric, activation during left-cathodal GVS. This issue has to be clarified in subsequent studies.

Together, these results suggest that the effects of GVS depend on the clinical characteristics of the sample *and* the stimulation parameters such as current strength and polarity which should be considered in the design of future studies.

In study 3 only online-effects during GVS were assessed as was done in all the other above-reported studies with GVS in neglect and related disorders, except in the study by Kerkhoff et al. (2011). This is currently the only available study reporting longer-lasting effects of GVS. Two case studies in patients with chronic left-sided tactile extinction, could show that one session of subliminal GVS reduced tactile extinction (Kerkhoff, et al., 2011). The obtained effects remained stable for at least one year (case 1) and three weeks (case 2) respectively. This study is the first hint, that longer-lasting improvements of neglect or neglect-related deficits are inducible by GVS, which is a prerequisite for establishing it as an effective treatment method for spatial neglect and related disorders. Because of the lack of studies on aftereffects of GVS, up-to-date studies on the physiological effects underlying such longer-lasting effects of GVS are not available either. One could only speculate about the effects referring to the evidence of long-term effects of the similar technique tDCS, whereby longer-lasting effects have repeatedly been found (Boggio, et al., 2007; Boggio, Rigonatti, et al., 2008; Fregni, Boggio, Nitsche, Marcolin, et al., 2006; Fregni, Gimenes, et al., 2006). The exact mechanisms are not entirely clear yet, but whereas for effects *during* stimulation changes of resting membrane potentials are assumed, *aftereffects* are believed to depend on synaptic modifications similar to the neuroplastic processes of long-term potentiation and long-term depression (for review see Stagg & Nitsche, 2011). In a rat stroke model Kim et al. (2011) showed

that anodal tDCS improved motor function without affecting infarct size, but reducing white matter axonal damage, indicating neuroprotective effects on neuronal axons. Because of the close similarity between tDCS and GVS, such mechanisms are presumably involved in GVS, too, suggesting neuroplastic and neuroprotective processes which the beneficial effects of GVS might be based on. Further studies are required both to replicate aftereffects of GVS and to elucidate their cellular basis, both in the intact and lesioned brain.

A limitation of Studies 2 and 3 of the present thesis is that GVS was only administered single-blind instead of double-blind carrying the risk of Rosenthal-effects, meaning that the subject's behaviour might be influenced by the experimenter's expectations (Rosenthal & Jacobson, 1968). The usage of a programmable direct current device, which guarantees that the experimenter is blind to the type of stimulation the participant receives, could circumvent such potential effects in future studies. However, this methodology usually requires additional personnel that either controls the programming of the device or completes the testing of the subjects. Another aspect concerning such a blinding procedure in patients is that higher current intensity (1.5mA in Study 3) was associated with more frequent itching during left-cathodal GVS than during sham stimulation in Study 2. Consequently, patients in Study 3 might have distinguished between those two stimulation conditions which could have influenced the observed results, such that the itching could have served as a spatial-attentional cue during left-cathodal GVS for orienting the attention to the neglected, left side of space. However, in Study 3 right-cathodal GVS was the more effective type of stimulation, which was not distinguishable via itching from sham or left-cathodal GVS as shown in Study 2. On the other hand, one could argue that the greater reduction of the line bisection error during right-cathodal GVS was due to the fact that this stimulation condition was not associated with itching, but that patients during left-cathodal GVS were distracted by the itching which could have led to an inferior performance during this type of stimulation. Nevertheless, there were significant differences in the line bisection performance of neglect patients during right-cathodal GVS and sham stimulation in Study 3, and both stimulation conditions were not distinguishable via adverse effects in Study 2, which argues against this interpretation of the data.

In general, such effects on subject blinding might be partially overcome by *subsensory* GVS[2], where experimental conditions are indistinguishable by their adverse effects (as the subject does not perceive the stimulation at all), which was shown to be sufficient for reducing tactile extinction (Kerkhoff, et al., 2011), line cancellation (Rorsman, et al., 1999) and visuoconstructive deficits (Wilkinson, et al., 2010). Alternatively, local anaesthesia of the skin or additional electrodes which induce skin sensation without eliciting vestibular sensations might be used to circumvent the problems with subject blinding (Lenggenhager, et al., 2008; Lopez, et al., 2010; see Discussion of Study 2 for further details).

6.3 Characteristics of Multimodal and Multispatial Deficits of Verticality Perception after Right-Hemispheric Stroke

In line with previous studies (Funk, Finke, Muller, Preger, et al., 2010; Saj, Honore, Bernati, et al., 2005), in Study 4 impaired verticality perception in two modalities and two spatial planes in patients with left-sided hemispatial neglect after right-brain damage were observed. Beyond those findings, the newly developed testing device used in Study 4 allowed the measurement of SV tilts in two modalities and two spatial planes with the same device allowing for unbiased comparisons between those parameters. The computed positive correlations between SVV and SHV as well as between SV tilts in roll and pitch indicate shared mechanisms underlying verticality perception in different modalities and different spatial planes. This is further corroborated by the direction of tilts in neglect patients. The settings of both the SVV and SHV were systematically tilted counterclockwise in the roll plane and analogously backwards in the pitch plane in right-brain-damaged patients with hemispatial neglect. These impairments are presumably due to lesions of the temporoparietal cortex associated with multisensory integration leading to a disturbed representation of the vertical.

The results relate to the questions raised in the introduction: Does verticality representation depend on certain brain areas or rather on the intactness of widely distributed neural circuits? If there is dependence on the lesion location, does that imply that there is a multimodal or even a-modal, and at the same time a multispatial or even a-

[2] However, one should keep in mind, that different stimulation strengths might induce different effects (see the discussion about different current strengths in line bisection above)

spatial central neural representation? This would mean that there is one brain area elaborating the representation of the SV in the visual, haptic and postural modality in the roll and pitch plane. Alternatively separate neural representations or both modality-/spatial plane-specific and multimodal/multispatial neuronal representations cold exist. Up to now, only one study on the SVV in the role plane using modern lesion analysis software (MRicro; Rorden & Brett, 2000) is available (Barra, et al., 2010), confirming the earlier results of Brandt et al. (1994) that lesions of the posterior insula and the neighbouring superior temporal gyrus or transverse temporal gyrus, are associated with SVV deficits in roll. However, other lesion locations were identified (see 1.1.1), even though without the use of modern lesion analysis techniques. A preliminary lesion analysis study on the SHV in roll identified lesions in the middle temporal gyrus to be associated with SHV tilts (Utz, Hildebrandt, et al., 2011). Based on findings on the SV in the visual, haptic and postural modality in stroke patients in which transmodal tilts were associated with right parietal lesions but dissociated with other lesion sites, Perennou et al. (2008) proposed that the right hemisphere elaborates an integrated verticality representation across different modalities.

The involvement of the parietal cortex in multisensory integration subserving the construction of an internal model of verticality is corroborated by a study using high-density evoked potentials in healthy individuals during SVV judgments. An early activation in the right lateral temporo-occipital cortex and later bilateral temporo-occipital and parieto-occipital activations were observed (Lopez & Blanke, 2011). The authors assume that the early component involving ventral visual stream is related to visual processing, and the later dorsal activation reflects multisensory integration to build an internal model of the vertical which is used for visuospatial processing and the control of actions and posture.

Furthermore, lesion size seems to influence the presence and severity of SVV (Barra, et al., 2010) and SPV (D. A. Perennou, et al., 2008) deviations. This observation together with the reported dissociations of SV tilts for all lesion sites except the parietal cortex, support the assumption that rather the disturbance of certain networks causes SV deficits than lesion of distinct brain areas (Barra, et al., 2010). Such circuits might involve thalamo-insular projections for vestibular graviception (D. A. Perennou, et al., 2008) and thalamo-parietal connections for somaesthetic graviception (Barra, et al., 2010).

Study 4 showed impaired verticality perception in two modalities and two spatial planes in right-brain-damaged patients with neglect, but not in right-brain-damaged patients without neglect or in healthy individuals. Does this mean that deficits of verticality perception critically depend on the presence of neglect per se? This question is highly debated in the literature (Johannsen, et al., 2006; Kerkhoff, 1998; Yelnik, et al., 2002). Most studies on the SV found that tilts of the SV were only apparent or at least larger in patients with hemispatial neglect compared to patients without neglect (Funk, Finke, Muller, Preger, et al., 2010; Funk, Finke, Muller, Utz, et al., 2010; Funk, et al., 2011; Gentaz, et al., 2001; Kerkhoff, 1999; Kerkhoff & Zoelch, 1998; D. Perennou, 2006; D. A. Perennou, et al., 2008; Saj, Honore, Bernati, et al., 2005; Yelnik, et al., 2002). In contrast, Johannsen et al. (2006) did not report a difference in SVV perception between patients with the pusher syndrome (i.e. active pushing away from the ipsilesional side with the ipsilesional arm or leg) and neglect vs. without neglect. Yet, the findings by Johannsen et al. (2006) might result from the additional pushing symptoms in the investigated neglect patients which might interact with other deficits and does not necessarily disprove the hypothesis that SVV tilts depend on the presence of hemispatial neglect. As an aside, Johannsen, et al. (2006) also reported a counterclockwise tilt (4.9°) in their neglect patients with pusher syndrome, which was however not statistically different from patients without neglect (2.6°).

The similar characteristics of both neglect and deficits of verticality perception can be seen as another argument supporting this assumption. Both disorders manifest themselves in different modalities. Hemispatial neglect occurs in the visual, haptic, auditory, and olfactory modality (Kerkhoff, et al., 2011), and deficits of verticality perception are prevalent in the visual and haptic modality (i.e. Study 4), as well as in the postural modality (D. A. Perennou, et al., 2008). The right parietal cortex is proposed to elaborate a verticality representation across different modalities (D. A. Perennou, et al., 2008) and the same brain area is believed to play a similar core role in the neglect syndrome, too (Fink, et al., 2000; Mort, et al., 2003; Vallar & Perani, 1986).

Furthermore, both disorders involve a disturbed integration of sensory input from different sources with the multimodal vestibular system playing a significant role in the processing of this information. Finally, stimulation of the vestibular cortical system via GVS was shown to reduce both neglect phenomena (i.e. Study 3) and SVV tilts (Saj, Honore, Bernati, et al., 2005; Oppenländer et al., unpublished results).

Consequently, one explanation for a potential causal link between neglect and SV tilts is that in neglect patients gravitational input might be processed asymmetrically leading to disturbed verticality perception (D. Perennou, 2006). This interpretation is supported by findings showing that SV judgments of neglect patients are strongly modulated by manipulations of sensory input such as changes of posture (Funk, Finke, Muller, Preger, et al., 2010) or lateral head inclination (Funk, Finke, Muller, Utz, et al., 2010) and GVS (Saj, Honore, Bernati, et al., 2005), in strong contrast to control patients or healthy individuals.

On the other hand, all those data do not necessarily imply a *causal* relationship between hemispatial neglect and deficits of verticality perception in general. It might also be conjectured, as proposed by Kerkhoff & Zoelch (1998), that distinct, but anatomical adjacent or overlapping regions are related to perturbed verticality perception and neglect, but that the typically very large lesions of the studied patients comprise both anatomical areas. Alternatively, the same authors propose a second scenario, whereby a lesion might affect a cortical network, processing information in different spatial planes, thus leading to SV deficits in the role and pitch plane as well as to neglect phenomena in the horizontal plane.

The results of Study 4 showing SV tilts only for the neglect patients rather suggest a potential causal link between neglect and SV tilts. To finally resolve this issue, detailed lesion analyses are required. Nevertheless, with regard to the clinical practice, the observed close relationship between neglect and deficits of verticality perception points to the need that SV deficits should be addressed specifically by diagnostics and treatments in patients with hemispatial neglect to improve their typically poor overall rehabilitation outcome. I will discuss further implications of these results for the clinical practice and neuropsychological research in the following section.

6.4 Implications for Clinical Practice and Neuropsychological Research

Neglect is a reliable predictor for long-lasting sensory-motor and cognitive impairments as well as a decreased functioning in activities of daily living (Katz, et al., 1999). For example, neglect patients show a stronger postural imbalance compared to other stroke patients (D. Perennou, 2006). As postural control is important for walking, walking

recovery takes longer in neglect patients (Gottlieb, Calvanio, & Levine, 1991). This is just one of many examples for the profound impairments of patients with hemispatial neglect, underlining the need for effective treatment methods. As GVS was shown to be associated with only minor adverse effects (Study 2) and to modulate, among other phenomena, the rightward line bisection error in neglect patients (Study 3), GVS seems to be suitable for repetitive therapeutic application. As outlined above (see section 6.2), GVS has many advantages compared to already existing stimulation techniques: GVS is not associated with unpleasant or even serious side effects in contrast to CVS and TMS. Furthermore it is relatively cheap, easy to use, has multimodal effects and may be used in combination with other treatment methods. Of course, this technique has to prove its effectiveness in further studies before becoming an approved treatment technique, but its easy application, its acceptance on the part of the patients in addition to its potential ability to induce long-term effects are encouraging.

The investigation of deficits of verticality perception after stroke has been comparatively neglected so far. Consequently their diagnostics and treatment have not yet been integrated into the clinical routine. Study 4 showed in a large sample of neglect patients that deficits of verticality perception occur in different modalities and different spatial planes and are correlated. The relevance of these impairments is underlined by their associations with difficulties in daily life such as mobility (Kerkhoff, 1999), clock reading and spatial dysgraphia (Kerkhoff, 1998), or body orientation to gravity (D. A. Perennou, et al., 2008). Moreover, SVV tilts are a predictor for poor balance recovery (Bonan, et al., 2007), as well as impaired ambulation capacity if a hemiparesis/hemiplegia is present (Bruell & Peszczynski, 1958; Bruell, et al., 1957). Accordingly, deficits of verticality perception after stroke need to be addressed in greater depth in neurorehabilitation. The "Haptic & Vision Meter" used in Study 4 allowing for unbiased measurement of SV tilts in two modalities and two spatial planes would be an ideal device for the diagnosis of deficits of verticality perception in the clinical practice. Concerning the treatment of those impairments, GVS was shown to transiently modulate SV deviations. Future studies should evaluate potential treatment effects of repetitive GVS on such SV tilts.

Compared to the relatively recent clinical use of GVS, the history of GVS as a research tool for investigating vestibular functions is much longer. Currently there is also a growing interest in using GVS for neuropsychological research in healthy subjects. For example, it has been shown that GVS increased response times in a mental transformation

task (Lenggenhager, et al., 2008), increased illusory fake hand ownership and the illusion of location of touch (Lopez, et al., 2010) and speeded up visual memory recall (Wilkinson, et al., 2008). GVS could moreover be used to investigate the vestibular influence on certain other neuropsychological disorders – beyond neglect and verticality perception. The evidence of good tolerance of GVS by healthy individuals and persons with stroke in Study 2 of the present thesis provides useful information for this purpose, too. Together with its relatively easy applicability, GVS seems to be ideally suitable both for neuropsychological research and rehabilitation.

6.5 Perspectives

There is growing evidence that GVS transiently modulates hemispatial neglect and related disorders. For clinical purposes, it is of interest to persistently ameliorate these deficits. Thus, future studies should investigate - ideally in randomised controlled trials - the long-term effects of repetitive GVS. Kerkhoff et al. (2011) showed for the first time long-lasting effects of GVS on tactile extinction which strongly points to the potential of GVS to persistently improve neglect and related disorders. It is likely that repetitive GVS leads to persistent improvements similar to other sensory stimulation techniques such as optokinetic stimulation (Kerkhoff, et al., 2006) or prism adaptation (Frassinetti, et al., 2002; Vangkilde & Habekost, 2010). In future clinical trials the effects of GVS on the patients' daily life should be assessed additionally, for example via standardised observation (questionnaires) or rating scales (i.e. the Catherine-Bergego-Scale; Bergego, et al., 1995) as assessed by relatives or clinical staff in order to increase the ecological validity of GVS as a treatment technique.

Another promising research approach for investigating therapeutic effects of GVS is the use of GVS as an add-on treatment for already established treatment methods. Previous studies using other sensory stimulation techniques have shown that the combination of different techniques such as visual scanning training and optokinetic stimulation (Schroder, et al., 2008) or visual exploration training and neck muscle vibration (Schindler, et al., 2002) are particularly effective. In the case of GVS, stimulation could increase the cortical excitability of brain areas which might enhance the effects of a simultaneously or sequentially performed behavioural training, such as visual exploration.

Thus, the combination of both methods might lead to stronger improvements as would do an isolated application of each technique.

With respect to the therapeutic effects of GVS, a further investigation of the surprising result of Study 3 would be interesting, namely that there was no significant difference between line bisection performance of neglect patients during 20 min left-cathodal GVS and after 40 s of left-cathodal GVS during the sham condition. We hypothesized that the short, initial current flow might have been strong enough to elicit a vestibular activation. If so, comparisons between the effects of short pulses of GVS and sessions of GVS lasting several minutes would be of interest and might considerably shorten the necessary treatment duration of GVS. This could maximize the efficacy of GVS as a sole or add-on treatment.

As GVS was shown to be associated with only very minor adverse effects (Study 2), this technique seems to be appropriate for repetitive application. Nevertheless, further studies on its safety are desirable particularly concerning longer stimulation durations (>20 min) and repetitive stimulations (10-30 sessions), including physiological data such as vestibulocochlear tests to complement the subjective indications of adverse effects as assessed in Study 2 via questionnaire.

Another issue being worth further investigation is the effect of GVS on the SV in patients with brain lesions (Saj, et al., 2006; Oppenländer et al., unpublished results). GVS was shown to ameliorate SV deviations both in the visual and the haptic modality in the role plane in neglect patients. It would be interesting to study whether GVS also modulates SVV and SHV deviations in the pitch plane. This is very likely, because it was shown that GVS is able to induce the sensation of illusory motion of one's body or the visual field in the roll, pitch, or yaw plane (Lopez, et al., 2010). Thus, GVS seems to act not only on multiple modalities, but also on different spatial planes.

With regard to the question whether there is a central neural representation of verticality perception and the relation to hemispatial neglect detailed modern lesion analyses are required. Lesion analyses is the method of choice in this context, because e.g. with fMRI, participants would lie and the supine position would influence the vestibular input and consequently the SV judgments (Funk, Finke, Muller, Preger, et al., 2010; Saj, Honore, Davroux, et al., 2005). Moreover, the poor spatial resolution of event-related potentials is not appropriate for the purpose of localisation.

6.6 General Conclusion

The studies presented in the present thesis indicate that GVS modulates multimodal neglect phenomena and related disorders and is well-tolerated by both healthy individuals and persons with stroke, with or without hemispatial neglect. Thus, GVS seems to be a suitable tool for neuropsychological research and a potential, promising treatment technique for the field of neurorehabilitation. The lack of serious side effects points to the applicability of GVS for repetitive stimulation in order to obtain longer-lasting improvements of hemispatial neglect and related disorders.

Furthermore, the present thesis provides evidence that deficits of verticality perception in patients with neglect, following right-hemispheric brain damage, are multimodal and multispatial in nature, and are closely related to the syndrome of neglect. These impairments suggest an altered representation of verticality most likely due to lesions of multisensory brain areas in the temporoparietal cortex.

As hemispatial neglect and deficits of verticality perception predict an adverse rehabilitation outcome, the research on underlying mechanisms and effective treatment methods is of crucial significance. The current thesis significantly contributes to those important aspects and paves the way for further research in this field.

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