Disorders of body cognition following unilateral stroke - neuropsychological basis and modulation by galvanic vestibular stimulation (GVS)

Dissertation

zur Erlangung des akademischen Grades eines

Doktors der Philosophie

der Philosophischen Fakultät III

der Universität des Saarlandes

vorgelegt von

Dipl.-Psych. Lena Schmidt

aus Saarlouis

Saarbrücken, 2014

Dekan: Univ.-Prof. Dr. Roland Brünken, Universität des Saarlandes

Berichterstatter: Univ.-Prof. Dr. Georg Kerkhoff, Universität des Saarlandes
Univ.-Prof. Dr. Thomas Schenk, Friedrich-Alexander Universität Erlangen-Nürnberg
Apl. Prof. Dr. Helmut Hildebrandt, Carl von Ossietzky Universität Oldenburg

Tag der Disputation: 04.06.2014

Abstract

Patients with vascular lesions of the right cerebral hemisphere often show unilateral, multimodal neglect. These patients fail to detect or respond to visual, acoustic or tactile stimuli in their contralesional hemispace or on their contralesional side of body. These failures are not caused by elementary disturbances of the visual (i.e. hemianopia), auditory (i.e. deafness) or motor (i.e. hemiparesis) modality, although they often go hand in hand with these impairments. The majority of previous studies have dealt with these sensory components of the syndrome, especially with *visual* neglect. However, there are many associated disorders with spatial neglect, e.g. impaired proprioception/arm position sense (APS) or tactile extinction.

Both disorders impair activities of daily living and predict a negative functional outcome with functional dependency after rehabilitation. Despite their frequent occurrence, few standardized measurements and suitable (long-term) treatment methods are available for these two impairments. A promising method for the treatment of hemineglect is galvanic vestibular stimulation (GVS), a non-invasive technique activating vestibular cortices and adjacent cortical areas, which are damaged in neglect patients. This method has recorded first successes, especially in visuospatial neglect and the related disorder of extinction. Moreover, previous studies focused almost exclusively on right-handers. Since left-handers show a different cortical organization of the vestibular system, which is crucially involved in body cognition, left-handedness should also be considered for diagnosis and treatment. Therefore, four studies were conducted in the present doctoral thesis, which address these aspects.

Study 1 focused on the immediate and after-effects (20 minutes) of subsensory, bipolar GVS on horizontal APS in stroke patients with versus without spatial neglect and matched healthy controls. The results showed that patients with neglect had an impaired contralesional (left) APS in contrast to the two other control groups. GVS decreased the errors in left APS during stimulation as well as 20 minutes after termination of GVS. As additional finding, right-cathodal/left-anodal GVS, resulting in right vestibular cortex activation, worsened left APS in the right-handed, healthy participants. This finding could refer to a right hemisphere specialization of the vestibular system - that is involved in APS - in right-handers as compared to left-handers, that is still under debate.

Therefore, Study 2 was operated in order to test the hypothesis that left- and right-handers differ in their anatomical representation of the vestibular system, namely that right-handers show a right hemisphere superiority and left-handers a left hemisphere dominance or a more bilateral, symmetrical organization. This was operationalized by studying the polarity-specific effects of GVS on APS in both forearms of right- and left-handers. Since the vestibular system is involved in somatosensory processing and the coding of body positions, GVS should affect this capacity differentially in both handedness groups. Right-cathodal/left-anodal GVS, resulting in right vestibular cortex activation, significantly deteriorated left APS in right-handers, but had no detectable effect on APS in left-handers in either arm. These findings are compatible with a right hemisphere dominance for vestibular functions in right-handers and a differential vestibular organization in left-handers that compensates for the disturbing effects of GVS on APS.

Study 3 was conducted to collect normative data of APS in healthy right-handers of different age groups with a novel device in order to diagnose and treat position sense disorders in clinical populations at a given time. APS was measured for both arms separately and the influences of age, sex and arm were analyzed. The results revealed that APS was not a function of age or sex but that APS was better in the non-dominant arm over all age groups. This indicates a right hemisphere superiority for left APS in right-handers and neatly fits to the more frequent and more severe left-sided body-related deficits in patients with unilateral stroke, e.g. impaired APS in left spatial neglect.

According to the positive effects of GVS on impaired APS in patients with neglect in Study 1, Study 4 evaluated the immediate and lasting effects (some 2.8 months) of GVS on another associated disorder that often co-occur with neglect, the tactile extinction. GVS improved tactile extinction in patients who received GVS but not in patients who were tested repeatedly but without receiving GVS. These results show a generic effect of GVS on tactile extinction, but not in a polarity-specific way that persisted at Follow-up.

In sum, the studies presented in this doctoral thesis afford new insights into the cortical vestibular organization of right- and left-handers, provide normative data for APS, reveal that APS is not a function of age or sex but that APS is better in the non-dominant arm over all age groups, document in two proof-of-principle studies the success of GVS as a long-lasting, effective treatment of impaired APS and tactile extinction in patients with stroke.

Content

Index of publications

The present dissertation is based on four international publications as first author. All publications are published as „original research articles“ in international peer-reviewed journals with high impact factor (Impact Factor IF, according to the Institute for Scientific Information ISI; 5-year IF for Neurorehabilitation and Neural Repair and Neuropsychologia, IF of 2012 for Frontiers in Human Neuroscience). The four studies are presented in chapters 3 to 6 of this thesis in their published form but adapted to the layout and number formatting of the present doctoral thesis. References for the four published studies are presented at the end of the doctoral thesis along with the literature of the present work.

Studies 1 and 4 are clinical studies that examine the potential of galvanic vestibular stimulation as a new treatment method in patients with impaired arm position sense (Study 1) and tactile extinction (Study 4). Study 2 examines the relationship between the cerebral organization of vestibular functions (in left- vs. right-handers) and its impact on the vestibular modulation of arm position sense. In Study 3 the effects of age, sex and arm on the precision of arm position sense were analyzed in a large sample of right-handers and normative data were collected with a novel diagnostic device for the assessment of arm position sense (Arm position device).

Study 1: Schmidt, L., Keller, I., Utz, K. S., Artinger, F., Stumpf, O., & Kerkhoff, G. (2013). Galvanic vestibular stimulation improves arm position sense in spatial neglect - A sham-stimulation-controlled study. *Neurorehabilitation and Neural Repair, 27*, 497-506. (IF: 4.877)

Study 2: Schmidt, L., Artinger, F., Stumpf, O., & Kerkhoff, G. (2013). Differential effects of galvanic vestibular stimulation on arm position sense in right- vs. left-handers. *Neuropsychologia, 51,* 893-899. (IF: 4.372)

Study 3: Schmidt, L., Depper, L., & Kerkhoff, G. (2013). Effects of age, sex and arm on the precision of arm position sense – left-arm superiority in healthy right-handers. *Frontiers in Human Neuroscience, 7:915*. doi: 10.3389/fnhum.2013.00915 *(*IF: 2.9)

Study 4: Schmidt, L., Utz, K. S., Depper, L., Adams, M., Schaadt, A.-K., Reinhart, S., & Kerkhoff, G. (2013). Now you feel both: galvanic vestibular stimulation induces lasting improvements in the rehabilitation of chronic tactile extinction. *Frontiers in Human Neuroscience, 7:90*. doi: 10.3389/fnhum.2013.00090 (IF: 2.9)

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Abbreviations

ADL	Activities of daily living
GVS	Galvanic vestibular stimulation
APS	Arm position sense
QET	Quality Extinction Test
CVS	Caloric vestibular stimulation
PIVC	Parieto-insular-vestibular-cortex
PET	Positron emission tomography
fMRI	Functional magnetic resonance imaging
mA	Milliampere
TENS	Transcutaneous electrical neural stimulation
L-GVS	Left-cathodal/right-anodal GVS
R-GVS	Right-cathodal/left-anodal GVS
RBD+N	Right brain-damaged patients with left-sided spatial neglect
RBD-N	Right brain-damaged patients without left-sided spatial neglect
C	Healthy control subjects
MRC	Medical Research Council
APD	Arm position device
AE	After-effect
ANOVAs	Analyses of variance
LTP	Long-term potentiation
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
UE	Unsigned errors
CE	Constant errors
AE	Absolute errors
DL	Difference limen
DSS	Double simultaneous stimulation
TP	Time-point of measurement
RPMS	Repetitive peripheral magnetic stimulation
LTD	Long-term depression
VST	Visual scanning therapy

1 Introduction

In Germany, stroke is the third most frequent cause of death. Although the high morbidity rate may be reduced by prevention campaigns (e.g. information about risk factors), there is a steadily increasing number of stroke patients with chronic disability who are in need of long-term care and assistance following their stroke. Due to the increasingly ageing society, this number will even rise in the next few years. Currently, about two percent of the expenses of statutory health insurance are needed for the treatment and care of patients with stroke (Stiftung Deutsche Schlaganfall-Hilfe, http://www.schlaganfall-hilfe.de/der-schlaganfall). Therefore, the development of (more) effective diagnostic and, especially, evidence-based appropriate treatments for impairments following stroke constitutes an important challenge for today and the near future.

Unilateral, multimodal neglect of the contralesional hemispace or side of body is a frequent and serious disorder, especially after right, middle cerebral artery infarction (e.g. 85% in Azouvi et al., 2002; Gottesman et al., 2008; Husain, 2008). It also occurs with a slightly minor frequency after left hemisphere lesions (e.g. 43.5% in Beis et al., 2004; Kleinman et al., 2007; Suchan, Rorden, & Karnath, 2012), but with similar severity (Suchan et al., 2012). The exact pattern of anatomical injury in patients with neglect depends on the clinical manifestation of neglect (Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010), clinical definition (core or satellite symptoms), chronicity (acute or chronic) and used method (structural or functional) (Karnath & Rorden, 2012). Worldwide, some three to five million patients after stroke suffer from neglect every year (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005). Patients with neglect ignore sensory stimuli (e.g. visual) located in the hemispace contralateral to the lesion side (Kerkhoff, 2001). In the past, the majority of studies have examined predominantly these sensory components of the syndrome, especially visual deficits, due to their most obvious emerging constraints in social environment and easy availability of assessment and treatment studies (Kerkhoff & Schenk, 2012). However, it becomes increasingly clear, that patients with neglect frequently show associated nonvisual impairments of body cognition that have received little attention so far in research (Jacobs, Brozzoli, & Farnè, 2012). Patients with neglect also suffer from deficits in identifying the spatial position of their contralesional, neglected arm in relation to the surrounding space or to their own body (= impaired proprioception/arm position sense; Vallar, Antonucci, Guariglia, & Pizzamiglio, 1993a; Vallar, Guariglia, Magnotti, & Pizzamiglio, 1995), or they ignore tactile stimuli on their contralesional side of body when simultaneously stimulated on the ipsilesional body side (= tactile extinction; Kerkhoff, Hildebrandt, Reinhart, Kardinal, Dimova, & Utz, 2011). Moreover, neglect after right hemisphere stroke is often associated with unawareness/anosognosia (Orfei et al., 2007; Vallar, Bottini, & Sterzi, 2003) which denotes the patient´s reduced or impaired insight into his/her impairments. Both spatial neglect and anosognosia for deficits predict a worse performance in standardized activities of daily living (ADL), a negative functional outcome and increased functional dependency after stroke (Appelros, Karlsson, Seiger, & Nydevik, 2003), as well as a generally negative outcome after rehabilitation (Eschenbeck et al., 2010; Jehkonen, Laihosalo, & Kettunnen, 2006; Kalra, Perez, Gupta, & Wittink, 1997; Kerkhoff & Schenk, 2012; Vossel, Weiss, Eschenbeck, & Fink, 2013). In recent years, progress has been made in neglect research, resulting in a consensus about the nature, symptoms and neuropathology of neglect, but there are still a lot of questions that need to be answered in future studies (Schenk & Karnath, 2012), e.g. therapies with long-term effects or the nature of satellite symptoms of neglect.

Another interesting point in research about body cognition in healthy subjects and patients with stroke is the almost exclusive concentration on right-handers, whereas left-handers or ambidexters were excluded. While this is understandable in terms of reducing the heterogeneity of the samples under study, it leads to a lack of relevant – also clinical – knowledge for the assessment and treatment of left-handed stroke patients. In fact, there is evidence that in left-handers the cortical vestibular system, which plays an important role in the area of body cognition, shows a different cortical organization as compared to right-handers. While left-handers are believed to show either a stronger lateralization in the left hemisphere (Dieterich et al., 2003) or a more bilateral representation (Linkenauger, Witt, Bakdash, Stefanucci, & Proffitt, 2009), right-handers show a right hemisphere vestibular dominance (Brandt & Dieterich, 1999). As a consequence, the resulting therapeutic methods, e.g. for proprioceptive impairments or spatial neglect after stroke, might be better suited for right-handers but less for left-handers. Hence, specific treatments for left-handers might be necessary.

Furthermore, there is a lack of precise, quantifiable and clinically suitable diagnostic instruments for the assessment of disordered body cognition, e.g. proprioceptive impairments after stroke (Connell & Tyson, 2012; Dukelow et al., 2010). While several technically sophisticated devices are available for the assessment of proprioception (e.g. in Jones, Fiehler, & Henriques, 2012; for a review, see Scott & Dukelow, 2011) most of them are expensive on the one side and time-consuming on the other side; together with the technical expertise required to operate these instruments, all these factors make it unlikely that they will be used in routine clinical assessment. Finally, few suitable treatment methods for the effective therapy of these disorders after stroke are available, and many of those published induce often only short-term effects whereas long-term effects are rarely reported (Kerkhoff & Schenk, 2012).

Therefore, apart from the other studies described in the present doctoral thesis, Study 3 reports the development, realization and empirical evaluation of a novel device developed specifically for the assessment of arm position sense in healthy right-handers (Study 3). Secondly, I studied the effects of a less well-known but very promising non-invasive brain stimulation technique, galvanic vestibular stimulation (GVS). Here, the effects of GVS for the short- and long-term modulation of impaired arm position sense following stroke (Study 1) and tactile extinction after stroke (Study 4) will be reported. Finally, GVS was used to explore potential differences in vestibular brain organization in right- versus left-handers and their impact on the modulation of arm position sense via GVS (Study 2).

In the following, I describe the theoretical background of the present doctoral thesis. This includes the presentation of three distinct disorders resulting from stroke – neglect, impaired arm position sense and tactile extinction – and of the human vestibular system, which is crucially involved in body cognition as well as of GVS as a potential treatment method for these disorders. Second, the four dissertation-relevant publications are presented in the subsequent chapters. The last part provides a general discussion of the present doctoral thesis, implications for neurorehabilitation and an outlook for prospective questions in this research field.

Figure 1 illustrates a graphical overview of the thematic affiliation of the particular studies in the context of rehabilitation following unilateral stroke.

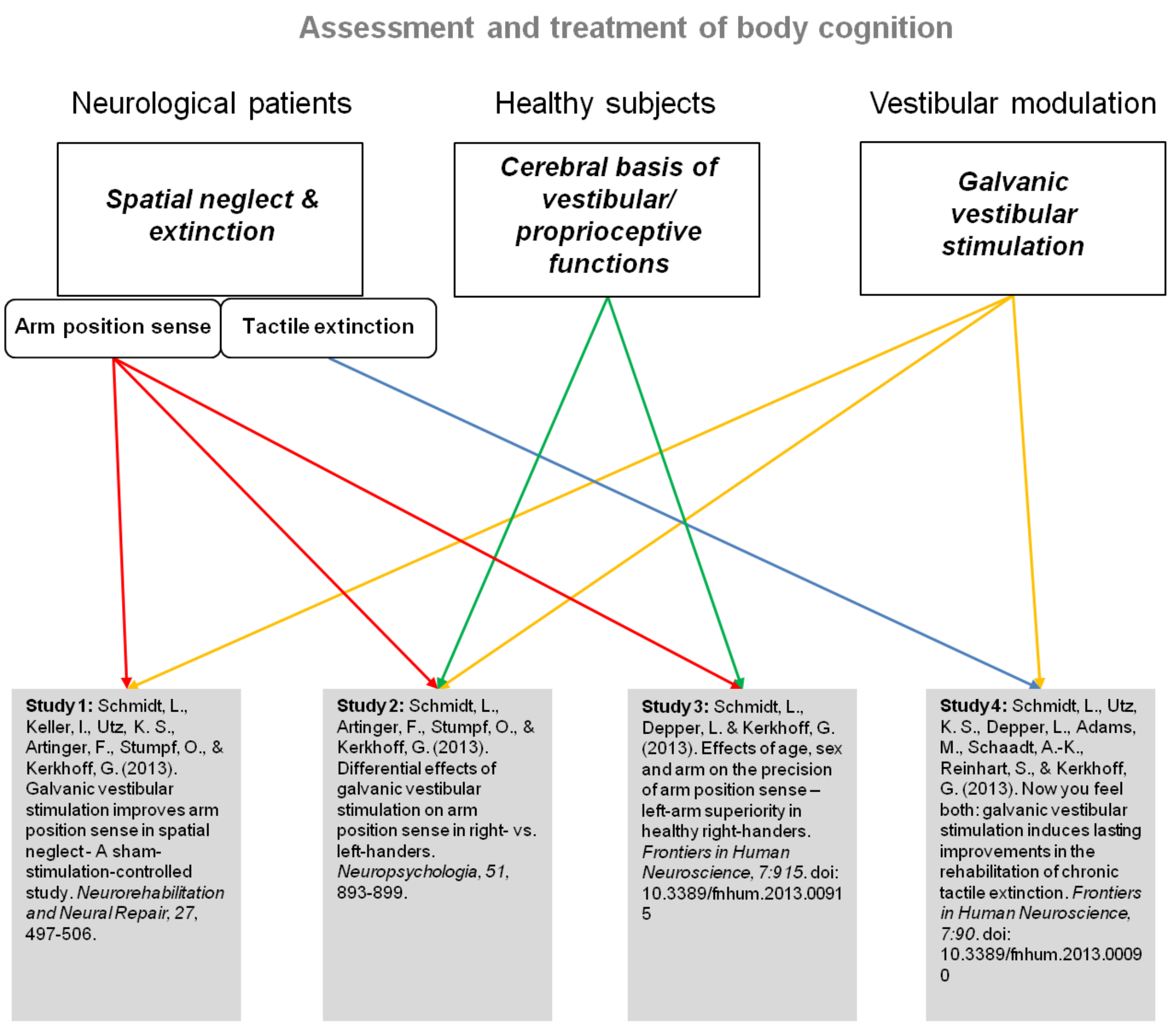


Figure 1 *Graphical overview of the thematic affiliation of the four studies which were conducted in the present dissertation.*

2 Theoretical background

This section gives a brief overview of spatial neglect and its associated deficits, i.e. impaired arm position sense and tactile extinction. Definitions, localization of brain lesions, diagnostic tools and therapeutic approaches are addressed subsequently in this chapter. Due to its important contribution to these disorders and relevance for potential therapies (i.e. GVS), the vestibular system is briefly described, followed by an introduction into the method of GVS.

2.1 Spatial neglect, impaired arm position sense and tactile extinction

Definitions

Spatial neglect is a neurological disorder defined as the inability to detect or process sensory stimuli (visual, auditory, tactile or olfactory) on the side of space contralateral to a lesioned cerebral hemisphere. Usually patients ignore left-sided stimuli due to right hemisphere lesions, but right-sided neglect after left hemisphere lesions occurs as well. Primary sensory – visual (hemianopia), auditory (deafness), somatosensory (touch impairment) – or motor deficits (hemiparesis, hemiplegia) as well as emotional (depression) or cognitive disorders (reduced intelligence) are by definition not causative for these neglect symptoms, although they often co-occur. Importantly, neglect is most often a *multimodal/multisensory* disorder (Jacobs et al., 2012) that can simultaneously affect different modalities related to the contralesional hemispace as well as to the contralesional side of the body. However, the multisensory nature of neglect as well as the question whether these deficits are functionally associated or dissociated on the behavioral and anatomical has to be clarified in future research (for reviews, see Jacobs et al., 2012; Kerkhoff, 2001).

The body-related neglect phenomena include e.g. body or motor neglect (Punt & Riddoch, 2006), proprioceptive deficits such as impaired limb position sense (Vallar et al., 1993a; Vallar et al., 1995) and tactile extinction (Kerkhoff, 2001) among others. Interestingly, they have been given little notice neither in previous research nor in the clinical and particular neurorehabilitative context (Punt & Riddoch, 2006; Reinhart et al., 2012).

Elementary, somatosensory impairments occur frequently after stroke and include e.g. impaired stereognosis, impaired proprioception and impaired tactile sensation (Connell, 2008). In the following, the two latter capacities will be considered in more detail.

Theses senses contribute e.g. to the dynamic interaction with the environment, to orientation and movement in space and to perform goal-directed motor actions and operations like grasping or manipulating objects in daily life (Carey, Oke, & Matyas, 1996; Fuentes & Bastian, 2010). Proprioception is defined as the ability to perceive the position and movement of one´s limbs without any visual information (Fuentes & Bastian, 2010). Proprioceptive disorders occur frequently after stroke, namely in 34-64% of the patients (Connell, 2008), and constitute besides visual disorders the most frequent sensory impairments after acquired brain lesions. Proprioceptive deficits are strongly associated with poor functional outcome after rehabilitation and negative consequences in many ADL (see Carey, 1995 for a review). Proprioception also includes limb position sense which denotes the ability to locate own limbs, e.g. legs, arms or fingers absolutely in space or in relation to the own body (Connell, 2008; Dukelow et al., 2010). Loss of limb position occurs in one third to half of stroke patients (Carey, 1995; Shah, 1978; Smith, Akhtar, & Garraway, 1983) and mostly affects the contralesional side of the patient´s body but can also affect the ipsilesional side (Sartor-Glittenberg & Powers, 1993; Vallar et al., 1993a; Vallar et al., 1995). Patients show grievous constraints in everyday life as in safety, postural stability and motor functions (Carey, 1995; Carey et al., 1996). In the clinical context, impaired *arm position sense* (further termed APS) is associated with a poorer and longer motor recovery of the hemiparetic or hemiplegic arm (De Weerdt, Lincoln, & Harrison, 1987; Feys et al., 2000; Kuffosky, Wadell, & Nilsson, 1982; Wade, Langton-Hewer, Wood, Skilbeck, & Ismail, 1983; Wadell, Kuffosky, & Nilsson, 1987). Traditionally, impaired APS was considered as a pure primary sensory deficit occurring with the same incidence after lesions to the right or left hemisphere (Reinhart et al., 2012; Shah, 1978; Vallar et al., 2003). In contrast, recent studies found a strong relationship between disordered APS, lesions to the right cerebral hemisphere and left spatial neglect (Vallar et al., 1993a; Vallar et al., 1995). Moreover, in general, impaired APS occurs more often after right hemisphere lesions as compared to left hemisphere lesions (Sterzi et al., 1993), as shown for spatial neglect, too. Both findings support the view of impaired APS as a higher-level disorder related to spatial neglect and with a common underlying mechanism of both disorders. A further striking analogy between impaired APS and spatial neglect is that both can be treated by the same methods of sensory stimulation. For instance, direction-specific leftward optokinetic stimulation, which means the coherent movement of visual stimuli to the contralesional side, improves position sense in patients with right hemisphere lesions as well as visuospatial neglect (i.e. in line bisection, length discrimination; cf. Schindler & Kerkhoff, 2004) in right-damaged patients (Kerkhoff et al., 2013; Kerkhoff et al., in press; see Kerkhoff & Schenk, 2012 for a review). This finding favors the assumption that position sense deficits in neglect have a non-sensory component: the neglect-related defective perception of the spatial position of body parts, as well as the ipsilesional derangement of unitary spatial representations both of body segments and objects in extrapersonal space (Vallar et al., 1993a). Therefore, a model of bodily perception (Vallar, Bottini, Rusconi, & Sterzi, 1993) was used to explain the abovementioned findings (Vallar et al., 1993a). According to this model, the incoming sensory (e.g. proprioceptive) information from each side of the body is first processed by each hemisphere separately, but with a stronger contralateral processing pathway. Second, the subsequently generated somatotopic representations are entered in an egocentric representation model of the body. Third, there is an interhemispheric asymmetry with a greater ipsilateral body representation of the right side of the body resulting in a higher susceptibility of this hemisphere for body-related deficits when lesioned by stroke. In patients with right hemisphere lesions this building-up and updating of the egocentric representation of their body and of their extra-personal space is perturbed (Vallar et al., 1993a). Due to the hemispheric asymmetry this model also can explain why neglect and impaired APS occur more frequently after right brain lesions.

Another phenomenon which is very often associated with neglect is extinction (Jacobs et al., 2012; for a detailed review, see also De Haan, Karnath, & Driver, 2012). Extinction is the inability to treat or process the more contralesionally located stimulus when two stimuli are simultaneously presented, regardless of the presented sensory modality. Primary sensory deficits are by definition not causative, resulting in an intact processing rate of a single stimulus when presented separately on each side (Kerkhoff, 2001). One type of extinction is sensory extinction that is defined as the disregard of a visual, auditory or tactile contralesional stimulus (Kerkhoff & Schenk, 2012). As shown for proprioceptive disorders in patients after stroke, extinction also occurs in the somatosensory/tactile modality, hence named *tactile extinction.* This form of extinction has been less often studied in previous research in contrast to *visual* extinction. However, tactile extinction occurs frequently after unilateral, mostly right hemisphere lesions (Heldmann, Kerkhoff, Struppler, Havel, & Jahn, 2000; Schwartz, Marchok, & Flynn, 1977; Schwartz, Marchok, Kremers, Kreinick, & Flynn, 1979). In daily life, intact touch is important for grasping, manipulating and identifying objects. In the clinical context, impaired somatosensory functions lead to longer length of stay and a reduced activity level (Winward, Halligan, & Wade, 1999). Moreover, tactile extinction is a negative predictor for the patient´s functional outcome after stroke (Rose, Bakal, Fung, Farn, & Weaver, 1994), probably because tactile information, as one important sensory source, provides feedback about the position of the limbs in space and in relation to the own body (see transformational hypothesis for neglect, below). Previously, extinction – as APS (see above) – was considered as a pure sensory deficit that occurs with the same incidence after right and left hemisphere lesions (Bender, 1952). However, the more frequent occurrence of extinction after right hemisphere stroke (Heldmann et al., 2000; Schwartz et al., 1977; Schwartz et al., 1979), the mostly intact elementary sensory abilities (Conci et al., 2009) and the fact that it frequently co-occurs with left spatial neglect (Kerkhoff & Schenk, 2012) contradict this explanation. Today, extinction is regarded as a satellite deficit related to neglect (Karnath & Rorden, 2012). In agreement with this, tactile extinction can be modulated by the same stimulation maneuvers as visuospatial neglect (e.g. caloric vestibular stimulation: Vallar et al., 1993b; optokinetic stimulation: Nico, 1999; prism adaptation: Maravita et al., 2003), suggesting a neglect-related component of the underlying mechanisms (Vallar, 1997; Kerkhoff, 2003).

The abovementioned phenomena have in common that patients show a strong non-use of their contralesional limbs exceeding their motor impairments following stroke. This behavior results in serious injury of contralesional limbs and a reduced functional outcome in the long-term after rehabilitation. Twenty-five percent of patients with left neglect maintain the typical symptoms and develop a chronic form of neglect (Karnath, Rennig, Johannsen, & Rorden, 2011; Rengachary, He, Shulman, & Corbetta, 2011). The remaining 75 % recover within the first six months after stroke (Hier, Mondlock, & Caplan, 1983; Jehkonen, Laihosalo, Koivisto, Dastidar, & Ahonen, 2007; Robertson & Halligan, 1999; Zarit & Kahn, 1974) but it is not clear whether the recovery includes *all* aspects of the syndrome or only the *most obvious* ones, which can easily be detected by available assessments (Kettunen, Nurmmi, Dastidar, & Jehkonen, 2012). Chronic patients show a greater functional disability than comparable patients without neglect, take longer to recover and show more associated impairments (Kalra et al., 1997; Punt & Riddoch, 2006). Neglect after acute right hemisphere stroke is also associated with several forms of cognitive deficits in contrast to comparable patients without neglect (Lee et al., 2008). Furthermore, patients with neglect are very often unaware of their symptoms and deny their problems, the so-called unawareness or anosognosia, that further aggravates the patient´s negative functional outcome (Cutting, 1978; Orfei et al., 2007; Vallar et al., 2003; Vossel et al., 2013). There is also a strong relationship between persisting anosognosia for hemiplegia in patients with peripersonal neglect and large right hemisphere lesions as well as greater cognitive impairment (Mattioli, Gialanella, Stampatori, & Scarpazza, 2012).

Assessment and diagnostic tools

Most studies, so far, focused on the development of diagnostic and therapeutic instruments for visuospatial neglect due to the easily accessible and practical assessment tools (i.e. paper-pencil tests, PCs) for this modality. However, nonvisual aspects of the neglect syndrome, namely haptic, body or motor neglect, or tactile extinction have been largely disregarded up to now, although they occur not less frequently than the visual symptoms. This focus on the visual modality in neglect research has led to a notable lack of diagnostic instruments for nonvisual, i.e. body-related neglect deficits (Kerkhoff & Schenk, 2012). In accordance with clinical research, my clinical experience also indicates that almost all patients with neglect symptoms report these impairments and feel strongly uncomfortable and insecure, and they, surprisingly, complain more intensively about these resulting limitations in daily life as compared to those resulting from their motor deficits.

Typically, limb or arm position sense is assessed by the experimenter or clinician moving the limb of the patient to a requested position (passive condition), or requiring the patient to move his/her limb to a target position (active condition), usually without vision. The latter active position sense tasks often include two paradigms: 'ipsilateral remembered matching task' where subjects have to remember and reproduce a target position of the same limb to which the limb was previously passively moved, and 'contralateral concurrent matching task' where subjects have to match the position of their limbs with the contralateral limb (Goble, Coxon, Wenderoth, Van Impe, & Swinnen, 2009). However, these tasks, first, require a certain degree of intact motor functions in the tested limb which is often reduced or simply absent in hemiplegic or hemiparetic patients, and, second, some basic cognitive capacities, i.e. attention and working memory (cf. Adamo, Martin, & Brown, 2007), which are also frequently impaired in patients following stroke. Therefore, assessment methods must take into account these motor and cognitive impairments (Carey et al., 1996). Another problem is that most diagnostic methods for limb position sense provide only ordinal or categorical ratings and give a subjective measure, such as pointing to different positions (Vallar et al., 1993a; Vallar et al., 1995), reaching movements (Gordon, Ghilardi, & Ghez, 1995), matching (Newport, Hindle, & Jackson, 2001; Van Beers, Sittig, & Denier van der Gon, 1998) or other new judgment tasks (Wilson, Wong, & Gribble, 2010). Some of them only use a three- (Sterzi et al., 1993) or four-point scale (Vallar et al., 1993a; Vallar et al., 1995), both being discrete scales and deliver only qualitative scores. These methods are not sensitive enough (Dukelow et al., 2010) for the diagnosis of small deviations in clinical population and for subtle, non-pathological deficits, e.g. in older adults (Vallar et al., 1993a; Vallar et al., 1995) or after modulation or therapy, only few of them produce robust data and are easy-to-use (Connell & Tyson, 2012). Moreover, they often lack age- and sex-specific normative data and psychometric criteria (Carey, 1995), so that it is not possible to make reliable and valid statements on position sense impairments in patients following stroke. Clinicians assess position sense merely by asking patients to distinguish whether their finger or toe is moved upward or downward by the experimenter (Bickley, 2012; Sterzi et al., 1993), finger finding, positional mimicry or two-point discrimination (Lincoln et al., 1991) as well as by using the thumb localizing task (Hirayama, Fukutake, & Kawamura, 1999). These clinical assessments also show no or poor psychometric criteria (e.g. interrater reliability), are not sensitive to subtle deficits and lack normative data (Carey, 1995; Garraway, Akhtar, Gore, & Prescott, 1976; Lincoln et al., 1991). However, recent studies show that there are some promising tools available for quantitative evaluation of sensorimotor functions of upper extremities. For example, robotic devices circumvent the abovementioned limitations of standard clinical assessment scales (for a review, see Scott & Dukelow, 2011). In this context, the bilateral robotic exoskeleton called KINARM (Scott, 1999), which measures horizontal limb position sense via mirror matching (Dukelow et al., 2010; Fuentes & Bastian, 2010) or reaching tasks (Coderre et al., 2010), is of interest. Another new method for assessing hand position sense is a magnetic motion tracking system with sensors attached on each hand in order to record movement trajectories in 3D coordinates (Leibowitz et al., 2008). Beside the advantages of such novel diagnostic devices for measuring limb position sense, they entail the risk of automatic movements without control for patients with motor impairments and a reduced flexibility in limbs (robotic devices). Additionally, they are too complex, expensive and time-consuming for routine clinical practice. As a consequence, such methods may be suitable for scientific research but will not be used in the clinical setting because of the abovementioned reasons. Hence, there is a need for an assessment tool for limb position sense which is easy-to-use and at the same time sensitive enough to detect performance changes during a treatment. Moreover, these tools should also be able to detect sub-clinical, pathological values. Carey and colleagues (see Carey et al., 1996; Carey, Matyas, & Oke, 2002 for more details) developed a quantitative measure of position sense called the Wrist Position Sense Test which meets the aforementioned criteria. Their approach was used to develop a novel test of APS with another joint (Carey et al., 1996).

Assessment of tactile extinction always includes unilateral trials on the left and right hand that may not be impaired, and double simultaneous stimulation on both hands that may be impaired on the contralesional side, and with both hands placed adjacent to each other on the table with the palms down (Kerkhoff, 2001). There are classical methods of double simultaneous stimulation e.g. by simply applying light touches on the dorsum of patients´ hands (Bender, 1952; Bender, 1977; used e.g. in Moscovitch & Behrmann, 1994), non-noxious electric shocks (Bueti, Constantini, Forster, & Aglioti, 2004; Guerrinin, Berlucchi, Bricolo, & Aglioti, 2003) or touches by solenoid devices (Kennett, Rorden, Husain, & Driver, 2010; Maravita et al., 2003). In contrast to such detection methods, there exist also more discriminative ways of extinction testing, e.g. by delivering different tactile stimuli to the hands which have to be identified, as in the Quality Extinction Test (QET; Schwartz et al., 1977; used e.g. in Heldmann et al., 2000; Kerkhoff et al., 2011a), or the naming of objects delivered to both hands simultaneously (Berti et al., 1999). In the latter assessment test, patients not only have to detect (the presence or absence of) tactile stimulation but also have to discriminate different haptic materials, which is more demanding than mere detection tests. It is therefore not surprising that the QET shows a greater sensitivity over the classical (detection) methods in revealing extinction phenomena in patients with stroke and a more subtle pathology (for a review, see Tucker & Bigler, 1989).

Therapy

Given the high frequency and the serious consequences for daily life, there is a substantial need for more effective therapies of the neglect syndrome and its associated impairments (Lincoln & Bowen, 2006). However, few or no treatments are currently available for these disorders that are capable of revising these symptoms permanently and completely, particularly in daily life. Nevertheless, several treatments lead to significant, though often temporary improvements, but show promising after-effects or at least a duration of treatment effects for some two to six weeks (see Kerkhoff, 2003; Kerkhoff & Schenk, 2012 for reviews). In general, there are two types of treatments for spatial neglect: top-down and bottom-up treatments. The first ones require patients to direct their attention actively to the neglected, mostly the left side. The main disadvantage of this treatment type is that it demands insight (awareness) and motivation from the patients, which are frequently reduced due to their associated anosognosia (see above).

Therefore, bottom-up treatments that are less dependent on insight or cooperation of patients with neglect were developed. These treatments are mostly based on sensory stimulation techniques and rely on the theory that the neglect syndrome results from an impaired representation and/or transformation of spatial coordinates into an outlasting, stable reference frame that is necessary for orientation in space (see Kerkhoff, 2001; Karnath, 2006 for overviews of neglect theories). This reference frame is based on incoming sensory information, e.g. visual, auditory, vestibular or proprioceptive, which are turned into a coherent body-centered spatial coordinate system that is important for orientation in space, visuomotor exploration and determination of our body position in space (Karnath, 1994b). The underlying idea of this theory is that a therapeutic manipulation of these sensory channels may correct the distorted spatial reference frame and, in turn, reduce neglect symptoms as well as related proprioceptive and somatosensory deficits. Recent treatment studies showed only temporary improvements of symptoms and included mostly *visual* aspects of neglect but paid little attention to other aspects of the syndrome such as motor, body-related or somatosensory deficits such as tactile extinction. However, recent studies showed that bottom-up treatments are able to improve both sensory neglect symptoms (transcranial magnetic stimulation: Oliveri, 2011; prism adaptation: Jacquin-Courtois et al., 2013; Newport & Schenk, 2012; optokinetic stimulation: Karnath, 1996; Kerkhoff, Keller, Ritter, & Marquardt 2006; Kerkhoff et al., 2012; Kerkhoff et al., 2013; Kerkhoff et al., in press; Pizzamiglio, Frasca, Guariglia, Incoccia, & Antonucci, 1990; vestibular stimulation: Karnath, 1994a; Utz, Keller, Kardinal, & Kerkhoff, 2011; Vallar et al., 1993b; limb activation: Robertson & North, 1993) as well as body-related neglect deficits, including impaired APS (optokinetic: Vallar et al., 1993a; Vallar et al., 1995; Vallar, Guariglia, Nico, & Pizzamiglio, 1997a; vestibular: Rode et al., 1992; Rode & Perenin, 1994; Rode, Tiliket, Charlopain, & Boisson, 1998; Vallar et al., 1993b; Vallar, Guariglia, & Rusconi, 1997b; Vallar et al., 2003; limb activation: Reinhart et al., 2012; Robertson, McMillan, MacLeod, Edgeworth, & Brock, 2002; Robertson & North, 1994) and tactile extinction (optokinetic: Nico, 1999; repetitive peripheral magnetic stimulation: Heldmann et al., 2000; prism adaptation: Maravita et al., 2003; limb position changes: Moro, Zampini, & Aglioti, 2004; vestibular: Vallar et al. 1993b) (for reviews, see Kerkhoff, 2001; Kerkhoff, 2003; Kerkhoff & Schenk, 2012).

However, many treatment studies presented only case studies, single session approaches, or show only transient improvements of symptoms. Moreover, randomized controlled treatment studies have been conducted rarely in this field. Furthermore, patients do not completely recover after rehabilitation and show many chronic disabilities in functional ADL even after treatment when they return home (Kerkhoff, 2001). Therefore, besides novel diagnostic instruments, there is also a lack of more effective therapeutic tools for long-lasting improvements of the multimodal and multicomponential neglect syndrome (Kerkhoff, 2003), particularly for the body-related aspects of it. Due to the limited duration of stay and restricted budget for clinical care, future treatment methods ideally should show long-term effects within shorter time periods and with low-cost equipment. To this purpose, new insights into the neuropsychological and anatomical basis of body-related functions in healthy subjects and neurological patients account for developing such treatments and, in turn, results of sensory stimulation methods provide additional information about human brain organization (Kerkhoff, 2003).

Some recent studies in the field of proprioception focused on lasting effects of sensory stimulation methods, e.g. on modulation of visual input. In a case study of Dijkerman, Webeling, Ter Wal, Groet and Van Zandvoort (2004), contralesional somatosensory impairments, namely pressure sensitivity and passive finger position sense, of a patient with neglect after stroke were treated successfully with two sessions of prism adaptation. She improved in her somatosensory deficits and this improvement persisted three weeks after prism adaptation, especially for her position sense. In two further studies, repeated sessions of optokinetic stimulation reduced visual neglect symptoms with an enduring effect up to 14 days (Kerkhoff et al., 2006), respectively two months (Kerkhoff et al., 2012) and auditory neglect (Kerkhoff et al., 2012). Other studies focus on vestibular modulation methods. Zubko, Wilkinson, Langston and Sakel (2013) examined whether five sessions of GVS induce persistent carry-over effects in two patients with visuospatial neglect. They found a significant improvement of performance in both patients that persisted for at least three days. In two other case studies, Kerkhoff and colleagues (2011a) found a lasting improvement of tactile extinction after a few sessions of GVS that lasted for more than three months, serving as an initial proof-of-principle study of the therapeutic efficacy of GVS. Recently, Utz, Keller, Kardinal and Kerkhoff (2011a) showed that one session of GVS can modulate, though temporarily, the pathological rightward line bisection bias in patients with left visuospatial neglect.

Therefore, GVS constitutes a promising method to modulate vestibular input in patients with neglect. To provide a theoretical basis for vestibular stimulation as treatment method for neglect used in the present doctoral thesis, first, the vestibular system is described and, second, GVS is specified in more detail.

2.2 The vestibular system

The vestibular system plays an important role in body cognition, including body representation and body self-consciousness (Ferrè, Vagnoni, & Haggard, 2013; Lopez, Schreyer, Preuss, & Mast, 2012). It allows recognition of the own position in space, perception of self-motion relative to the external space and the detection of movements in space (for an overview, see Dieterich, 2006), e.g. as a kind of sensory signal management system that detects changes in the relation between the body and the external environment (Ferrè, Bottini, Iannetti, & Haggard, 2013). The vestibular system enables postural stability (e.g. of the head and trunk), spatial orientation and gaze stabilization by processing sensory input coming from motor responses to position of the body, head and eyes as well as body and limb movements relative to the environment (Fitzpatrick & Mooney, 2012). To this purpose, it combines information from different sensory systems, especially visual, auditory, somatosensory and proprioceptive inputs (Brandt & Dieterich, 1999) and projects to different brain areas which, in turn, combine these different inputs to give a definite representation of orientation and movement in space, and position of body in the environment (Bottini et al., 1994). Most studies use vestibular stimulation methods, e.g. GVS or caloric vestibular stimulation (CVS), in healthy individuals or patients as well as in behavioral or neuroimaging studies in order to identify vestibular brain areas (see below). They found that vestibular processes occur in thalamocortical vestibular pathways including vestibular nuclei in the brainstem, thalamic nuclei, cerebellum and the cortical “vestibular cortex” (for reviews, see Fitzpatrick & Mooney, 2012; Khan & Chang, 2013; Lopez & Blanke, 2011; Lopez, Blanke, & Mast, 2012; Zu Eulenburg, Caspers, Roski, & Eickhoff, 2012) which will be described in the following.

Peripheral vestibular system

The peripheral vestibular system is comprised of two vestibular organs, which are used to detect acceleration due to gravity. They are located on the right and the left side behind the ear in the hard bone of the skull, embedded in the inner ear. Each vestibular organ consists of three semicircular canals and two otolith organs, which are connected with the cortex and with the processus mastoideus via cells of mastoid (Fitzpatrick & Day, 2004; Schünke, Schulte, Schumacher, Volle, & Wesker, 2006). Their afferent and efferent nerves are bunched within the nervus vestibularis, which links the peripheral vestibular system with the central vestibular system via nervus vestibulo-cochlearis (Fitzpatrick & Day, 2004; Trepel, 2004). Information from the peripheral vestibular system are ascending to the thalamocortical network via vestibular pathways (Zwergal, Strupp, Brandt, & Buttner-Ennever, 2009).

Central vestibular system

The central vestibular system comprises subcortical and cortical structures. It encloses a network of brainstem, cerebellar, thalamic and cortical areas involved in the processing, integration, and perception of graviceptive information (Dieterich et al., 2003; for reviews, see Lopez & Blanke, 2011; Lopez et al., 2012a). Information about rotational and translational accelerations of the vestibular organs is passed to the brain and combined in the brainstem with other sensory and motor systems which is important for gaze control and postural stability (Trepel, 2004). The first relay station of vestibular information from peripheral vestibular organs occurs in the vestibular nuclei in the brainstem. These nuclei are connected with other nerves and nuclei in the reticular formation, with the cerebellum, oculomotor nuclei and the hypothalamus. The vestibular information passes further through the thalamus and finally reaches the cerebral cortex (Fitzpatrick & Day, 2004; Trepel, 2004).

There is still little knowledge about the homologous vestibular cortex areas of the human cortex. In non-human primates studies, the vestibular system includes somatosensory areas (area 2v, 3av), intraparietal sulcus, posterior parietal cortex (area 7), area MST, frontal cortex, cingulum and hippocampus (Lopez & Blanke, 2011) and the parieto-insular-vestibular-cortex (PIVC) (Guldin & Grüsser, 1998; Lopez & Blanke, 2011). Strong interconnections exist between these multisensory regions, but the PIVC is the only vestibular cortex area that receives information from all other areas of the cortical vestibular system as well as from vestibular nerves in the brainstem and, therefore, serves as a core integration area (Grüsser, Pause, & Schreiter, 1990a; Grüsser, Pause, & Schreiter, 1990b; Guldin, Akbarian, & Grüsser, 1992; Guldin & Grüsser, 1998). In the PIVC the vestibular input converges with other sensory signals and contributes to spatial orientation and navigation. This assumption is approved by the fact that vestibular stimulation of the semicircular canals and the otolith organs activates the PIVC, and optokinetic visual stimulation leads to a deactivation of this region due to the reciprocal inhibitory visual-vestibular interaction (for a summary, see Dieterich, 2006). Studies in primates suggest that in contrast to other sensory modalities such as visual or auditory, there is no single vestibular cortex but rather an “inner circle of the vestibular cortex” including the abovementioned multisensory areas and subserving vestibular information, among others. In the last years, many studies aimed to identify the human homologue of the primate PIVC. A recent meta-analysis found a joint vestibular network in accordance with this concept in humans, too (Zu Eulenburg et al., 2012). They found temporal, parietal and insular cortices, as well as the putamen and thalamus, processing vestibular information and forming a distributed, cortical vestibular system (for reviews, see e.g. Lopez & Blanke, 2011; Lopez et al., 2012a). Neuroimaging studies of the human vestibular system propose e.g. the posterior insula in the depths of the lateral sulcus and the temporo-parietal junction (Bense, Stephan, Yousry, Brandt, & Dieterich, 2001; Bottini et al., 1994; Bucher et al., 1998; Lobel, Kleine, Bihan, Leroy-Willig, & Berthoz, 1998; Stephan et al., 2005) or the parietal operculum (Eickhoff, Weiss, Amunts, Fink, & Zilles, 2006; Ferrè, Bottini, & Haggard, 2012; Zu Eulenburg et al., 2012) as possible candidates for the human homologue of PIVC, but the exact location is still under debate (Lopez & Blanke, 2011).

Furthermore, vestibular information is processed bilaterally, but with a greater emphasis on the right hemisphere in right-handers (Suzuki et al., 2001; Dieterich et al., 2005; Eickhoff et al., 2006; Zu Eulenburg et al., 2012; Arshad, Nigmatullina, & Bronstein, 2013). In contrast, there is a lack of knowledge concerning the cortical organization and lateralization of vestibular functions in left-handers. In one of the few studies dealing with different handedness groups, Dieterich et al. (2003) found in a PET study that CVS activates the vestibular system bilaterally on a subcortical and cortical level, but with a dominance of the non-dominant hemisphere in both handedness-groups, the right hemisphere in right-handers and left hemisphere in left-handers. They argued that the vestibular system and its cortical projections influence the development of handedness. Janzen et al. (2008) also found in a fMRI study the importance of the hemispheric preponderance in processing of vestibular information in both handedness groups. In the first behavioral study, Arshad and colleagues (2013) also demonstrated that vestibular cortical processing is strongly lateralized to the non-dominant hemisphere due to an asymmetrically modulated vestibular-ocular reflex. There is also evidence that prenatal asymmetry of the peripheral vestibular system may predict handedness and cortical vestibular lateralization (Previc, 1991). In a recent animal study, Best and colleagues (2013) found a strong left hemispheric dominance of vestibular processing independent of handedness in rats, and they interpreted this finding as evidence of an early hemispheric specialization in ontogenetic older species. In sum, the direction of the correlation between handedness and vestibular lateralization is still unclear and should be subject, or at least one subsidiary aspect, of future research.

Figure 2 shows the human vestibular areas identified by imaging studies in healthy subjects using different vestibular stimulation methods and the equivalent vestibular areas found in animals.

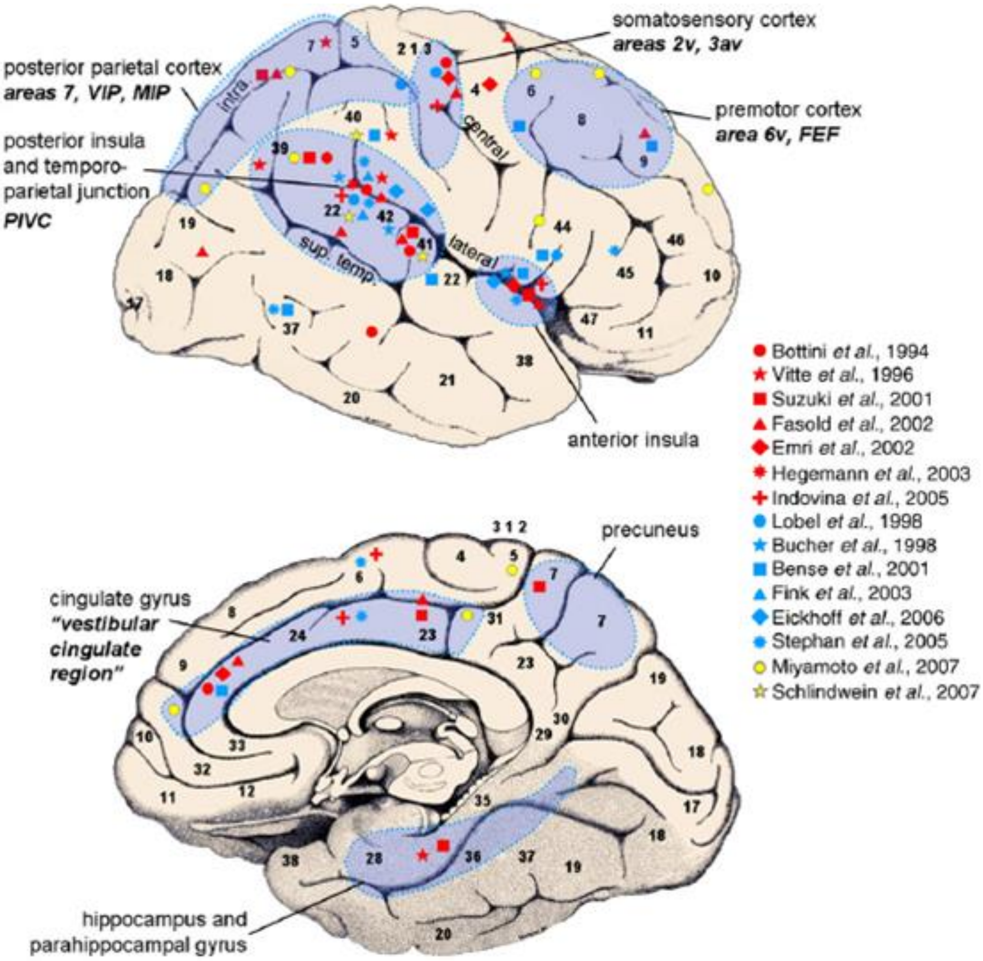


Figure 2 *Anatomy of the human vestibular cortex. Vestibular areas in humans revealed by neuroimagery during caloric (red symbols) and galvanic (blue symbols) vestibular stimulation, as well as during short auditory stimulation (yellow symbols). To summarize, right and left cerebral activations are reported 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. Abbreviations: FEF: frontal eye fields; MIP: medial intraparietal area; MST: medial superior temporal area; PIVC: parieto-insular vestibular cortex; VIP: ventral intraparietal area. The numbers on the cortex refer to the cytoarchitectonic areas defined by Brodmann. Figure 3B in "The thalamocortical vestibular system in animals and humans", by C. Lopez and O. Blanke, 2011, Brain Research Reviews, 67, 119-146.*

2.3 Galvanic vestibular stimulation

Galvanic vestibular stimulation (GVS) has a long history in experiments on animal and human electricity (for a review, see Utz, Dimova, Oppenländer, & Kerkhoff, 2010) and has been used for probing the primate and human vestibular system (for a review, see Fitzpatrick & Day, 2004). This non-invasive stimulation technique consists of applying weak direct currents via two electrodes of different polarity placed on the mastoid bones behind the ears. Most commonly used is bilateral bipolar stimulation, meaning that the anodal electrode is placed on one mastoid and the cathodal electrode on the other mastoid (Fitzpatrick & Day, 2004). As mentioned above, the vestibular nerves run underneath the mastoids form the inner ear towards vestibular brainstem nuclei, and further to the thalamic relay station (for a review, see Utz et al., 2010). Bilateral bipolar GVS affects via polarization effects the discharge pattern of the vestibular nerve, the otolith organs, as well as the semicircular canal afferents and finally the human homologue of the PIVC (Fitzpatrick & Day, 2004). Functional imaging studies of GVS using direct current stimulation (Bense et al., 2001) and alternating current (Lobel et al., 1998; Stephan et al., 2005) have shown that GVS activates the posterior insula, temporo-parietal regions, the middle and superior temporal gyrus, the anterior cingulated gyrus, the putamen and the thalamus, which most of them are involved in the processing of vestibular information (Lopez & Blanke, 2011; Lopez et al., 2012a).

In Figure 3, a schematic illustration of the mechanisms and main anatomical pathways and brain sites including subcortical and cortical relay stations of GVS via stimulation of the mastoids are depicted.

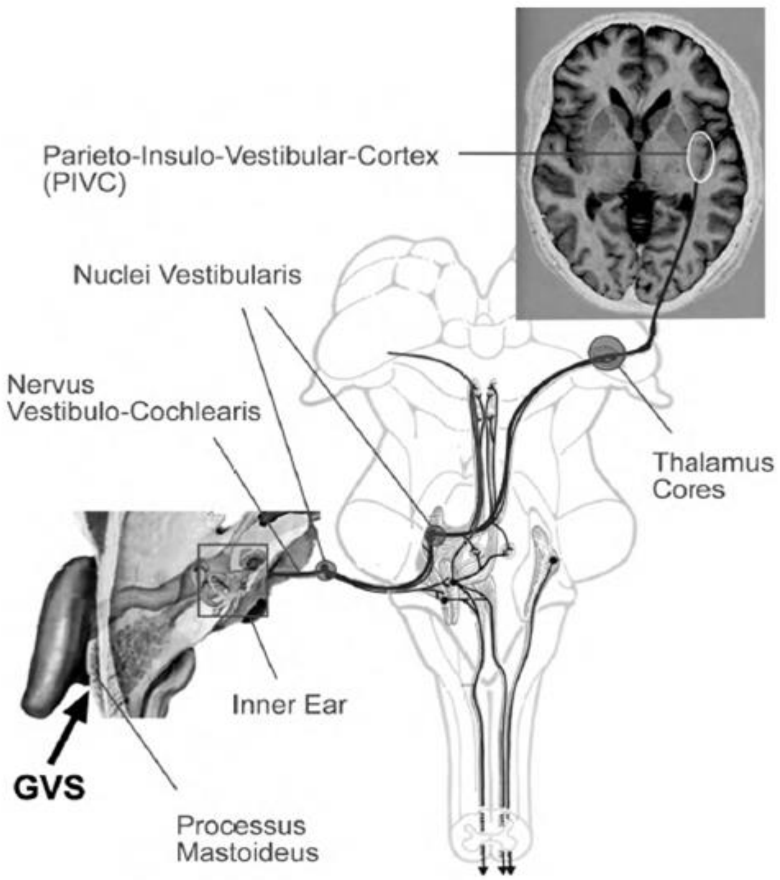


Figure 3 *Schematic illustration of the mechanisms of galvanic vestibular stimulation (GVS). Stimulation at the mastoids (see arrow) activates the vestibular nerve, and subsequently all vestibular relay stations located upstream including nervus vestibulo-cochlearis, vestibular nuclei in the brainstem, thalamic nuclei and finally the parieto-insular-vestibular-cortex (PIVC), as well as adjacent areas such as the temporo-parietal junction and the parietal cortex (not indicated). Figure 3 in “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” by K.S. Utz, V. Dimova, K. Oppenländer, G. Kerkhoff, 2010, Neuropsychologia, 48, 2789-2810.*

Furthermore, the position of the anode and cathode produces different effects on polarization and activation processes (Rinalduzzi, Cipriani, Capozza, & Accornero, 2011). In right-handers, galvanic inhibition of the left vestibular nerve with excitation of the right vestibular nerve (right-cathodal/ left-anodal GVS) results in right vestibular cortex activation, whereas galvanic inhibition of the right vestibular nerve with excitation of the left vestibular nerve (left-cathodal/right-anodal GVS) activates the vestibular cortex bilaterally (Fink et al., 2003).
Another vestibular stimulation method is CVS which activates only the horizontal semicircular canal (Dieterich et al., 2003) and is often accompanied by side effects as nystagmus and vertigo. In contrast, GVS activates both the otoliths and the semicircular canal (Bortolami, Inglis, Castellani, DiZio, & Lackner, 2010; Curthoys & McDougall, 2012; Stephan et al., 2005). Therefore, *single* sessions of subthreshold and suprathreshold GVS cause only mild adverse effects, no vertigo, nausea or gross nystagmus, and only rarely feelings of uncomfortableness in post-stroke patients and healthy individuals (Utz et al., 2011b), when safety guidelines are followed (Utz et al., 2010). Moreover, recent single-case studies suggest that *repeated* sessions of GVS are also tolerable for patients following stroke (Wilkinson, Zubko, & Sakel, 2009; Zubko et al., 2013). In sum, GVS is a low-cost, easy-to-use and well-tolerable promising technique suitable for rehabilitation in patients. Moreover, subsensory or sham-stimulation in neuroscientific research is easier to realize as compared to other stimulation methods, e.g. transcranial magnetic stimulation, because subjects are unaware of the applied condition (Utz et al., 2010).
Figure 4 shows the anatomical vestibular areas of healthy subjects activated by different vestibular stimulation methods.

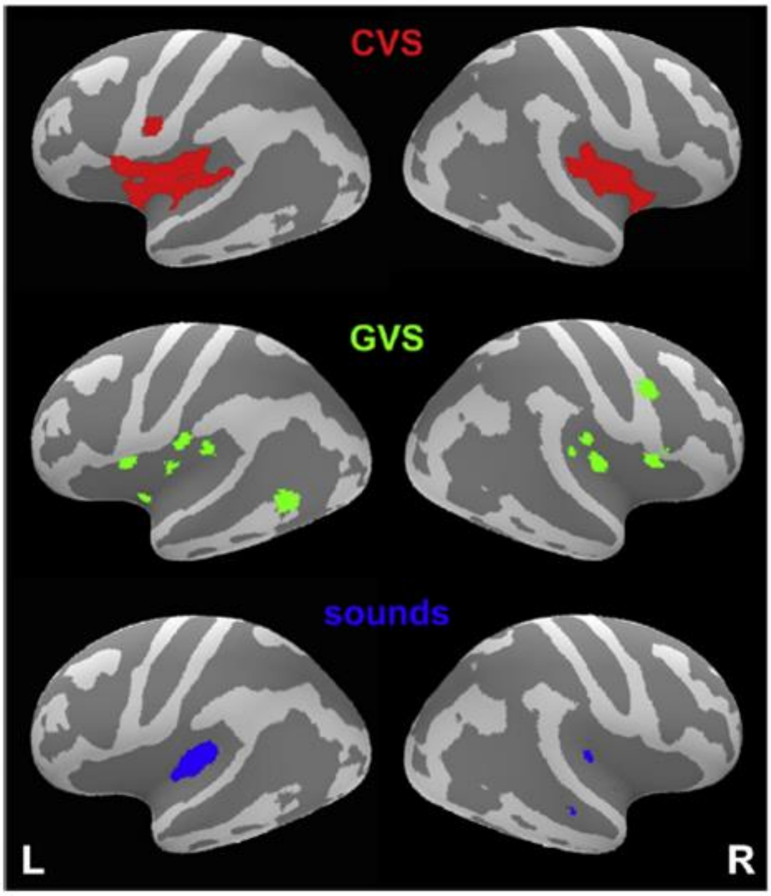


Figure 4 *Localization of significant clusters identified by the meta-analysis for CVS (Analysis 1), GVS (Analysis 2), and sounds (Analysis 3) irrespective of the side of the stimulation . Results are displayed on inflated hemispheres to reveal activations in the Sylvian fissure. All values are corrected for false discovery rate (P<0.05). Abbreviations: CVS: caloric vestibular stimulation; GVS: galvanic vestibular stimulation. Figure 3 in "The human vestibular cortex revealed by coordinate-based activation likelihood estimation meta-analysis" by C. Lopez, O. Blanke, F.W. Mast, 2012, Neuroscience, 212, 159-179.*

In the following sections 3 to 6, the four dissertation-relevant studies 1 to 4 are presented.

3 Study 1: Galvanic vestibular stimulation improves arm position sense in spatial neglect - A sham-stimulation-controlled study

Schmidt, L., Keller, I., Utz, K. S., Artinger, F., Stumpf, O., & Kerkhoff, G. (2013). *Neurorehabilitation and Neural Repair, 27*, 497-506.

3.1 Abstract

Disturbed APS is a frequent and debilitating condition in patients with hemiparesis after stroke. Patients with neglect, in particular, show a significantly impaired contralesional APS. Currently, there is no treatment available for this disorder. GVS may ameliorate neglect and extinction by activating the thalamocortical network. The present study aimed to investigate the immediate effects and after-effects (20 minutes) of subsensory, bipolar GVS (M = 0.6 mA current intensity) on APS in stroke patients with versus without spatial neglect and matched healthy controls. A novel opto-electronic arm position device was developed, enabling the precise measurement of the horizontal APS of both arms. In all, ten healthy controls, seven patients with left-sided hemiparesis and left-spatial neglect, and 15 patients with left hemiparesis but without neglect were tested. Horizontal APS was measured separately for both forearms under four experimental conditions (baseline without GVS, left-cathodal/right-anodal GVS, right-cathodal/left-anodal GVS, Sham-GVS). The immediate effects during GVS and the after-effects 20 minutes after termination of GVS were examined. Patients with neglect showed an impaired contralateral APS in contrast to patients without neglect and healthy controls. Left-cathodal/right-anodal GVS improved left APS significantly, which further improved into the normal range 20 minutes poststimulation. GVS had no effect in patients without neglect but right-cathodal/left-anodal GVS worsened left APS in healthy participants significantly. GVS can significantly improve the impaired APS in neglect. Multi-session GVS can be tested to induce enduring therapeutic effects.

3.2 Introduction

Patients with right hemisphere stroke often show left-sided spatial neglect (Husain, 2008). Neglect occurs mostly after right (Husain, 2008), middle cerebral artery infarction (Husain, 2008; Gottesman et al., 2008), and its symptoms may persist for years (Hier et al., 1983; Zarit & Kahn, 1974). Patients with neglect fail to detect or respond to sensory stimuli in their contralesional hemispace and tend to underutilize their contralateral limbs. They suffer from greater functional disability than stroke patients without neglect and therefore take longer to recover despite comparable stroke pathology and motor impairments (Kalra et al., 1997). The associated unawareness aggravates this unfavorable outcome (Cutting, 1978; Orfei et al., 2007; Vallar et al., 2003). By definition, elementary sensory or motor deficits are not causative of neglect but often co-occur with the disorder.

Right brain damage, neglect and deficits of arm position sense

In the past, the majority of studies investigated visual neglect while non-sensory, body-related neglect phenomena (i.e. body and motor neglect, proprioceptive deficits (Vallar, et al., 1993a; Vallar et al., 1995), impaired identification of body parts and motor extinction) have received less attention (Reinhart et al., 2012; see also review in Punt & Riddoch, 2006). Deficits in APS are common after stroke (Shah, 1978; Smith et al., 1983) and were traditionally considered to be primary sensory disorders (Reinhart et al., 2012; Shah, 1978; Vallar et al., 2003). Recent studies, however, found a strong correlation between right hemisphere stroke, spatial neglect and impaired APS (Vallar et al., 1993a; Vallar et al., 1995). Moreover, impairments in APS were found to occur more often after right than left brain damage (Sterzi et al., 1993). This hemispheric asymmetry fits observations of a higher incidence of neglect following right- versus left-sided stroke.

Furthermore, the cortical representations of each side of the body are mainly located in the contralateral hemisphere with only a minor body representation in the corresponding ipsilateral hemisphere. Interestingly, the ipsilateral representation of the left body side is less elaborated in the left cerebral hemisphere (Vallar et al., 1993b), rendering the left body side more susceptible to body-related deficits such as an impaired position sense after a lesion of the right hemisphere. This may explain why patients with neglect perform worse in APS tasks than patients without neglect (Vallar et al., 1993a; Vallar et al., 1995). In this context, it is also noteworthy, that leftward optokinetic stimulation transiently improves contralateral APS by some 12-20% (Vallar et al., 1993a; Vallar et al., 1995) which points to a neglect-related component in the spatial coding of body parts and shows how this impairment might be modulated.

Clinically, impairments in locating one’s own limbs without visual feedback are associated with imprecise motor functions, reduced spontaneous use of arms, awkward limb positions, reduced safety and postural instability (Carey, 1995). In neglect, deficient position sense impedes motor functioning and is related to left motor neglect (Vallar et al., 2003).

One theory hypothesizes that neglect results from an impaired representation/transformation of spatial coordinates into an egocentric reference frame, necessary for correct body orientation in space (Halligan, Cockburn, & Wilson, 1991; Jeannerod & Biguer, 1987; Karnath, 1994b). Right cerebral lesions perturb the updating of such egocentric representations for body and space (Vallar et al., 1993a). Recent advances in neglect therapy are based on sensory stimulation techniques which partly rely on these theories (Kerkhoff, 2003) and show that optokinetic stimulation (Kerkhoff et al., 2012; Vallar et al., 1993a), prism adaptation (Pierce & Buxbaum, 2002; Rossetti et al., 1998), neck muscle vibration (Schindler, Kerkhoff, Karnath, Keller, & Goldenberg, 2002) and CVS (Kerkhoff & Schenk, 2012; Rode, Perenin, Honoré, & Boisson, 1998) all reduce visual neglect (Kerkhoff & Schenk, 2012). Unfortunately, motor (Punt & Riddoch, 2006) and body-related deficits in patients with neglect have been virtually ´neglected´ in therapy research in the last two decades. These types of impairments are not negligible as for example 20% of patients with right hemisphere stroke show motor neglect (Buxbaum et al., 2004), and 32% an impaired position sense (see results) without any treatment currently available. In light of the overall negative motor outcome of patients with neglect (Perennou, 2006), their impaired postural control (Perennou, 2006) and the well-known proprioceptive deficits of the left body side (Vallar et al., 1993a; Vallar et al., 1995), effective treatments for these nonvisual disorders associated with neglect are urgently required to accelerate a more complete functional recovery beyond the achievements gained in visual neglect. How can this goal be achieved?

TENS transiently improves neglect-related postural instability selectively in patients with left neglect (Perennou et al., 2001). Moreover, Dijkerman and colleagues (2004) recently demonstrated lasting improvements in proprioception after prism exposure in a patient with left neglect. These studies show a significant modulation of nonvisual disorders in left neglect. GVS is another promising, non-invasive technique activating vestibular, motor and adjacent cortices as well as subcortical areas involved in postural, spatial and cognitive functions (for a review, see Lopez & Blanke, 2011). Recently, we showed that one 20-minute session of GVS temporarily reduces the ipsilesional bias in line bisection in patients with visuospatial neglect (Utz et al., 2011a), and two sessions improve tactile extinction permanently by about 40% (Kerkhoff et al., 2011a). Accordingly, CVS reduces left motor neglect (Rode et al., 1992; Rode et al., 1998a). GVS, unlike CVS, is easier to use, lacks adverse side effects and is more appropriate for repetitive treatment without habituation effects (Utz et al., 2011b; Utz et al., 2010). Practically, weak direct currents are delivered via two electrodes of different polarity (anode and cathode) placed on both mastoids behind the ears (Fitzpatrick & Day, 2004). GVS activates the whole thalamocortical system up to the PIVC (Fitzpatrick & Day, 2004; Lopez et al., 2012a) which is partly damaged in neglect (Mort et al., 2003). Bi-hemispheric activations are obtained by applying left-cathodal/right-anodal GVS (further termed L-GVS), whereas unilateral, right-hemispheric activations are induced by right-cathodal/left-anodal GVS (further termed R-GVS) (Fink et al., 2003). GVS might thus modulate deficits in APS in a similar way as TENS or prism goggles in the abovementioned studies.

The present study addressed the following issues:

(i) Does GVS modulate APS in both forearms in stroke patients with versus without neglect differentially, and does it lead to an immediate- (online-effect) as well as after-effect (20 min post GVS)? The inclusion of the right brain-damaged patients without left-sided spatial neglect is clinically important because it may signal the specificity of GVS to a certain subgroup of stroke patients (i.e. those with left neglect). Moreover, differential effects might tell the clinician which patient might potentially improve (under GVS) and which not.

(ii) Are there polarity-specific effects of GVS on APS, similar to those found for tactile extinction (Kerkhoff et al., 2011a) or line bisection (Utz et al., 2011a)?

3.3 Methods

Subjects

Seven patients with right hemisphere stroke and left-sided visuospatial neglect (six males, RBD+N), 15 patients with right brain damage but without neglect (14 males, RBD-N), and 10 age-matched, healthy control subjects (seven males, C) were included (Table 1). Inclusion criteria for all patients were a single, supratentorial, right hemisphere stroke, right-handedness and awareness of (left) hemiparesis. Exclusion criteria were bilateral or left-sided lesions, aphasia and psychiatric disorders in addition to specific GVS exclusion criteria (heart pacemaker, pregnancy, metallic brain implants, epilepsy or sensitive skin behind the ears) (Utz et al., 2011b). The three subject groups did not differ with respect to age (χ^2 (df=2) = 2.57, p = .276), and sex (χ^2 (df=2) = 2.49, p = .288). The two patient samples were neither significantly different in the severity of the somatosensory (U = 51.5; z = -0.12, p = .91) and motor impairments (hemiparesis; U = 29.5; z = -1.74, p = .08), nor in time since lesion (U = 28; z = -1.73, p = .08). Proprioception was examined by requiring patients to imitate arm postures during neurological assessment and was found to be normal in all patients. All participants gave their informed written consent before examination. The study was approved by the local ethics committee (Ärztekammer München, Germany). All subjects were right-handed (Salmaso & Longoni, 1985), had no history of psychiatric disorders or dementia, showed good awareness of their hemiparesis and had a corrected visual acuity of at least 0.5 (50%, distance 0.4 m; Table 1).

Table 1 *Clinical and demographic data of seven patients with left neglect due to a single vascular lesion of the right cerebral hemisphere (RBD+N1 to RBD+N7), and 15 patients with a single right hemisphere vascular lesion without neglect (RBD-N1 to RBD-N15) . Abbreviations: RBD+N: right brain-damaged patients with left-sided neglect; RBD-N: right brain-damaged patients without left-sided neglect; ICB: intracerebral bleeding; m: male, f: female; PCI: posterior cerebral artery infarction; MCI: middle cerebral artery infarction; Neglect tests: L: left, R: right; Line bisection: + = rightward deviation, - = leftward deviation; Visual acuity: binocular, decimal letter acuity for the near viewing distance (0.4 m; 1.0=100%=20/20 Snellen equivalent). Cut-off scores for neglect screening tests: > 4 omissions in the star and letter cancellation task; > 5 mm in line bisection, < 6 points in figure copying; > 2 reading errors and/or >120 seconds reading time in the paragraph reading test.*

Patient	Age/Sex	Etiology	Months since lesion	Left Neglect	Visual Acuity Near	Neglect dyslexia	Star cancellation omissions L/R, max. (27/27)	Letter cancellation omissions L/R, max. (20/20)	Line bisection (20 cm, deviation in mm)	Figure copying	Somatosensory impairment	Motor impairment	Unawareness of hemiparesis
RBD+N1	41/m	ICB	28	yes	0.8	yes	0/2	2/2	+7	9	3	4	no
RBD+N2	72/m	ICB	72	yes	0.8	yes	3/3	3/1	+3	8	0	1	no
RBD+N3	44/f	ICB	77	yes	1.0	yes	0/0	1/2	+15	9	0	4	no
RBD+N4	81/m	MCI	3	yes	0.5	yes	27/22	20/13	+89	0	0	1	no
RBD+N5	58/m	MCI	0.5	yes	0.5	no	5/0	16/2	-1	8	0	0	no
RBD+N6	70/m	MCI	41	yes	0.63	yes	3/3	3/2	-3	5	0	4	no
RBD+N7	66/m	MCI	**3**	yes	0.8	yes	4/2	4/2	+13	2	0	3	no
Mean	**61.7 (SD=14.8) years**		**32.1 (SD=32.7)**		**0.7 (SD=0.2)**		**6/5**	**6/2**	**+17.6 (SD=37.6)**	**6**	**0**	**2**	
RBD-N1	76/m	MCI	0.5	no	0.8	no	0/0	0/2	+2	8	0	5	no
RBD-N2	71/m	MCI	1.5	no	0.6	no	0/0	1/0	-13	9	0	3	no
RBD-N3	84/m	MCI	1	no	0.8	no	0/0	0/0	+1	9	0	4	no
RBD-N4	54/m	ICB	33	no	1.0	no	0/0	0/1	+3	9	3	4	no
RBD-N5	83/m	ICB	4	no	0.5	no	9/2	0/4	-5	8	1	0	no
RBD-N6	50/f	MCI	1	no	1.25	no	0/0	0/1	-7	9	0	5	no
RBD-N7	56/m	ICB	1.5	no	1.0	no	0/0	0/4	-2	9	0	5	no
RBD-N8	76/m	ICB	1	no	1.0	no	2/1	5/6	-2	7	0	4	no
RBD-N9	74/m	ICB	2	no	0.6	no	1/0	0/1	-5	8	0	4	no
RBD-N10	64/m	PCI	28	no	0.8	no	0/0	1/2	-10	6	0	4	no
RBD-N11	70/m	MCI	1.5	no	0.8	no	0/0	0/0	0	9	0	4	no
RBD-N12	73/m	MCI	13	no	1.25	no	2/2	0/0	0	8	0	4	no
RBD-N13	58/m	MCI	4.5	no	0.8	no	1/1	0/0	-1	9	0	3	no
RBD-N14	63/m	MCI	1.0	no	1.0	no	0/1	0/1	2	7	0	4	no
RBD-N15	43/m	MCI	20	no	1.0	no	0/0	0/0	2	7	0	2	no
Mean	**66.3 (SD=12.2) years**		**7.6 (SD=10.8)**		**0.9 (SD=0.2)**		**1/0**	**0/1**	**-2.3 (SD=4.8)**	**8**	**0**	**4**	

Assessment of somatosensory and motor impairment, unawareness and neglect

All patients were assessed with a standard somatosensory function screening of the contralateral (left) upper limb yielding scores on a four-point scale ranging from 0 (no defect) to 3 (severe impairment). While the eyes of the patients were closed, the examiner administered with his fingertip 10 single and 10 double, symmetrical and simultaneous tactile stimuli, as shortly and lightly as possible, on the dorsal surface of the patient´s hands. Tactile extinction was only recorded when more than 90% of unilateral tactile stimuli were correctly reported. Motor impairment of the forearm was measured using the Medical Research Council (MRC) Scale (Guarantors of Brain, 2000; Gurd, Kischka, & Marshall, 2010). This scale grades muscle strength on a scale from 5 (no defect) to 0 (severe impairment). Unawareness of reduced muscle strength in the contralesional forearm was tested with Cutting´s anosognosia questionnaire (Cutting, 1978), with a rating scale ranging from 0 (spontaneous reporting) to 3 (Cutting, 1978). Visuospatial hemineglect was assessed by five screening tests: star cancellation, letter cancellation, line bisection and figure copying (Fels & Geissner, 1997; Wilson, Cockburn, & Halligan, 1987). Furthermore, a paragraph reading test (180 words) (Kerkhoff et al., 2012) was carried-out (for cut-off scores see Table 1). All screening tests were performed with the centre of the display positioned perpendicular to the mid-sagittal plane of the patient´s trunk. The results in all tests were used to calculate a combined neglect severity index (from 0 = normal performance in all 5 tests to 5 = abnormal results in all 5 tests). Patients were classified as showing neglect with a score of ≥ 2.

Assessment of arm position sense

APS in the horizontal plane was measured with an opto-electronic apparatus (“arm position device”, APD, see Figure 5). The APD consisted of a 90° circuit table with a manually adjustable LED lamp for optical indication of the required arm position. A movable armrest on a 90° circuit below the table was installed under the circuit of the lamp in order to locate the subject´s current horizontal arm position with a resolution of 1°. Furthermore, a control panel stored the difference (in °) between the target position and the actual arm position during the experiment. The subjects were sitting in front of the apparatus with the right or left arm on the armrest. The subject’s forearm was moved manually by the examiner with an average velocity of 4.3°/s (range: 3.6-5.8°/s) towards two different angle positions (30° and 60°) from four different starting positions: 90° (straight ahead), 60°, 30°, 0° (Figure 5). The experimenter did not see the actual position of the arm support or the patient´s arm because he directed his gaze to the periphery of the APD in order to avoid experimenter bias. There were 12 trials (three per position) for each arm and two practice trials that were not scored. The sequence of trials varied randomly across subjects with the right forearm being tested first in every subject. In each trial, the subjects were required to indicate verbally as precisely as possible when their forefinger was directly positioned under the LED. During the experimental session, the arm and shoulder of the individual were covered by a black cape and the testing room was darkened (1 Lux) to reduce any visual cues. No time constraints were imposed and no feedback was given. Measurements were performed following a schedule (controlled by stopwatch) thus lasting 20 minutes per session. The criterion measure for APS was the unsigned, average positional error, expressed as the absolute difference between the actual arm position and the target arm position as indicated by the LED (in degrees, averaged over 12 trials/condition). The unsigned cut-off scores for healthy controls were 4.6° for the right and 4.2° for the left forearm (based on n = 24 right-handers, age range: 51-71 years).

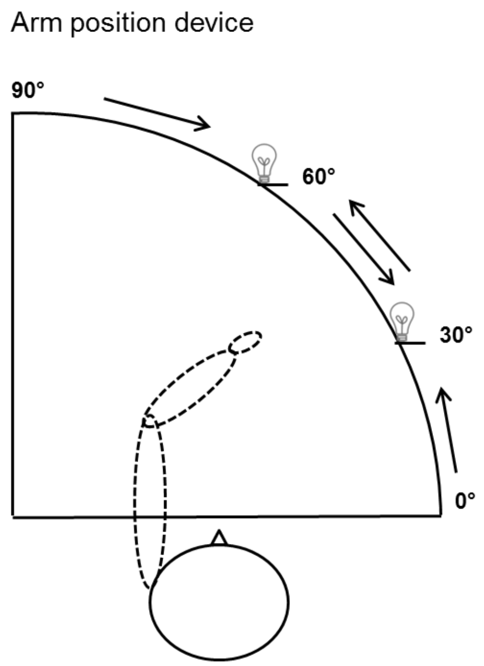


Figure 5 *Schematic view of the apparatus used for measuring arm position sense in the study and of the patient´s position when the left forearm was tested - two different angle positions (30° and 60°) from four different starting positions: 90° (straight ahead), 60°, 30°, 0° are shown.*

Galvanic vestibular stimulation

Subjects were stimulated with a nine-voltage battery-driven constant direct current stimulator (neuroConn GmbH, DC-Stimulator, 98693 Ilmenau, Germany). Bilateral bipolar GVS was performed by placing two carbon electrodes (anode and cathode) over both mastoids. The electrodes (50 x 35 mm) were inserted in saline-soaked sponges. The polarity of the applied electric currents was changed between three experimental conditions. For L-GVS stimulation the cathode was placed on the left mastoid and the anode on the right mastoid. This electrode setup was reversed for the R-GVS condition. In the Sham condition, the two electrodes were positioned as in the L-GVS condition, except that no electric current was applied. For subliminal GVS, the individual sensory threshold for stimulation was determined in session 1 by progressively increasing the current amplitude in steps of 0.1 mA until the subjects reported a tingling sensation underneath the electrodes. The current was then decreased until the cutaneous sensation stopped. This procedure was repeated twice so that a current intensity of 0.1 mA below the mean value at which the tingling sensation occurred was selected for subliminal stimulation. The mean current amplitude used for subliminal GVS in the patients was 0.6 mA. The duration of subsensory GVS was limited to a maximum of 20 minutes, in order to conform to established safety guidelines (Utz et al., 2010).

Design and Procedure

All subjects participated in four different experimental sessions (Figure 6). In session 1, all screening assessments (see *Assessment of somatosensory and motor impairment, unawareness and neglect*) and the first Baseline test in horizontal APS were carried out. In session two to four, the subjects performed the APS task again while receiving either L-GVS, R-GVS or Sham-GVS, respectively in a pseudo-randomized sequence to control for order effects. Subjects were blind to the type of stimulation received. In each stimulation session, the electrodes were removed after 20 minutes of stimulation (alternatively Sham stimulation) and the subjects paused for 20 minutes in darkness. After 20 minutes, the APS was measured again to evaluate potential after-effects (= AE). A two day interval (min. 48 hours) was established between sessions to avoid carry-over effects.

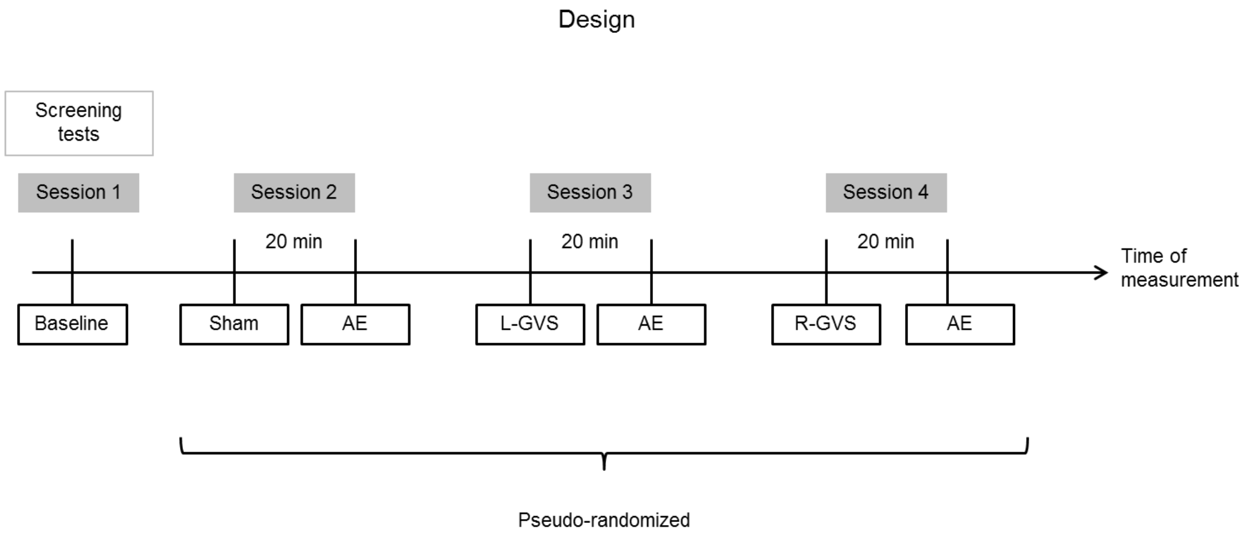


Figure 6 *Design of the study with the four different experimental sessions: L-GVS: left-cathodal/right-anodal GVS; R-GVS: right-cathodal/left-anodal; AE: after-effect.*

Statistical analyses

All analyses were carried out using SPSS, version 19. First, the APS scores of the 12 trials per condition were averaged. Analyses of variance (ANOVAs) with the between factor “group” (C, RBD+N, RBD-N) and the within factor “GVS condition” (Baseline, Sham, Sham-AE, L-GVS, L-GVS-AE, R-GVS, R-GVS-AE) were carried out separately for the right and left arm. Significant results were followed-up with Bonferroni-adjusted t-tests for multiple comparisons (Holm, 1979). The alpha-level was set at p = .05, two-tailed for all analyses.

3.4 Results

Figure 7 A and B display the online- and after-effects of GVS on APS, separately for both arms and across all experimental conditions in the three subject groups.

Right arm

The analysis of the performance of the right arm did not show a statistically significant main effect of GVS condition ($F(6,102) = 0.73$, $p = .555$, $\eta^2 = .025$) or group ($F(2,29) = 0.95$, $p = .398$, $\eta^2 = .062$) or a significant GVS condition × group interaction ($F(12,102) = 0.652$, $p = .713$, $\eta^2 = .043$) (see Figure 7 A).

Left arm

By contrast, the analyses of the APS scores of the left arm yielded a significant main effect of GVS condition ($F(6,119) = 3.13$, $p = .017$, $\eta^2 = .097$) and a significant interaction between GVS condition and group ($F(12,119) = 2.55$, $p = .013$, $\eta^2 = .15$). No significant main effect was found for the factor group ($F(2,29) = 2.99$, $p = .066$, $\eta^2 = .171$). Subsequent t-tests analyzing the APS differences between GVS conditions were computed for each group separately. For the C-group the analyses revealed a significant deterioration in APS in the R-GVS condition as compared to Baseline ($T(9) = -3.78$, $p = .004$), Sham ($T(9) = -7.82$, $p = .000$), Sham-AE ($T(9) = 3.24$, $p = .01$) and L-GVS-AE ($T(9) = -4.14$, $p = .003$). Moreover, the deviations of the healthy control subjects were larger in the R-GVS-AE condition than in the Sham ($T(9) = -4.99$, $p = .001$) and L-GVS-AE condition ($T(9) = -3.46$, $p = .007$). The APS error was also more severe in the Sham-AE ($T(9) = -2.95$, $p = .016$) and L-GVS condition ($T(9) = -2.26$, $p = .05$) as compared to the Sham condition. Furthermore, the RBD+N patients showed significantly smaller deviations in the L-GVS condition ($T(6) = 2.45$, $p = .05$) and a further enhancement in the L-GVS-AE condition ($T(6) = 3.59$, $p = .012$) as compared to Baseline. Additionally, they also improved significantly in both L-GVS ($T(6) = 7.39$, $p = .000$) and L-GVS-AE ($T(6) = 3.94$, $p = .008$) relative to Sham. In the RBD-N-group, however, no significant differences in APS across conditions were found (all Ps > .127). Subsequent t-tests analyzing the GVS condition x group interaction showed that deviations of the RBD+N patients at Baseline and during Sham-GVS were significantly larger than those of the C-group (Baseline: $T(11) = -2.69$, $p = .021$, $d = -3.21$; Sham: $T(8) = -3.07$, $p = .015$, $d = -3.79$) and of the RBD-N-group (Baseline: $T(10) = 2.69$, $p = .023$, $d = 3.07$; Sham: $T(9) = 2.32$, $p = .044$, $d = 2.99$) (see Figure 7 B).

In summary, RBD+N patients were significantly impaired in their left APS. This deficit improved significantly during L-GVS (p=.05) and further into the normal range 20 min after cessation of L-GVS (p=.012). Control subjects showed a significant deterioration of their left arm's APS during R-GVS (p=.000). All these effects were significant when compared with Baseline and Sham conditions, suggesting that these findings do not result from learning, test repetition or other unspecific effects.

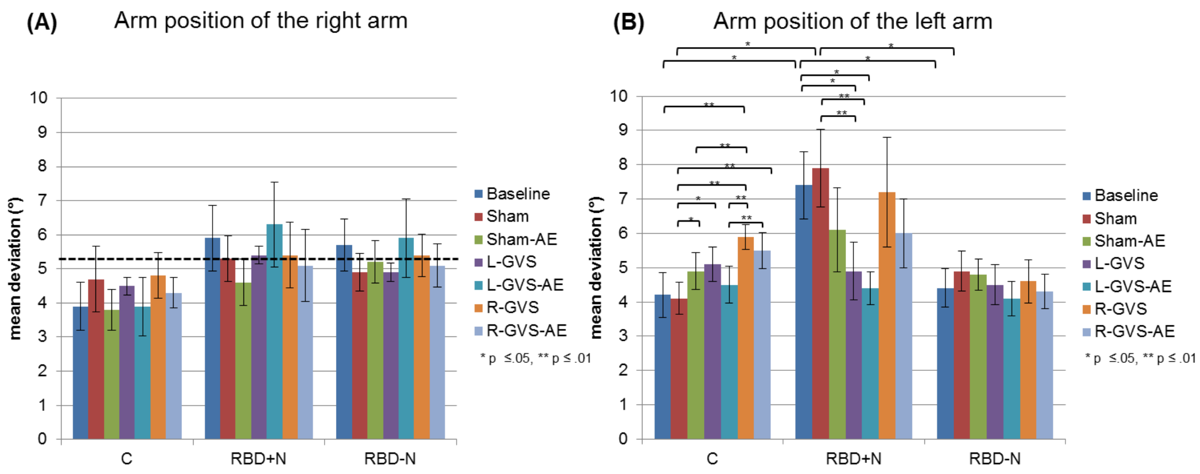


Figure 7 *Mean unsigned errors (in degrees) and standard error of the mean (SEM) of the three subject groups in the different experimental conditions of right and left arm; Online- and after-effects of the right **(A)** and left arm **(B)** and the respective cut-off scores of healthy control subjects (dashed lines, n = 24, right arm: 4.6°, left arm: 4.2°). Abbreviations: C: healthy control subjects; RBD+N: right brain-damaged patients with left neglect; RBD-N: right brain-damaged patients without left neglect; L-GVS: left-cathodal/right-anodal GVS; R-GVS: right-cathodal/left-anodal GVS; AE: after-effect.*

Figure 8 shows the individual results of all seven patients with neglect of the left arm position as a function of lesion chronicity. All patients showed their best performance during L-GVS and L-GVS-AE (after-effect), independently of chronicity. Patient 4 showed more variable results and an additional improvement in APS during R-GVS and R-GVS-AE which was not found in the other six patients.

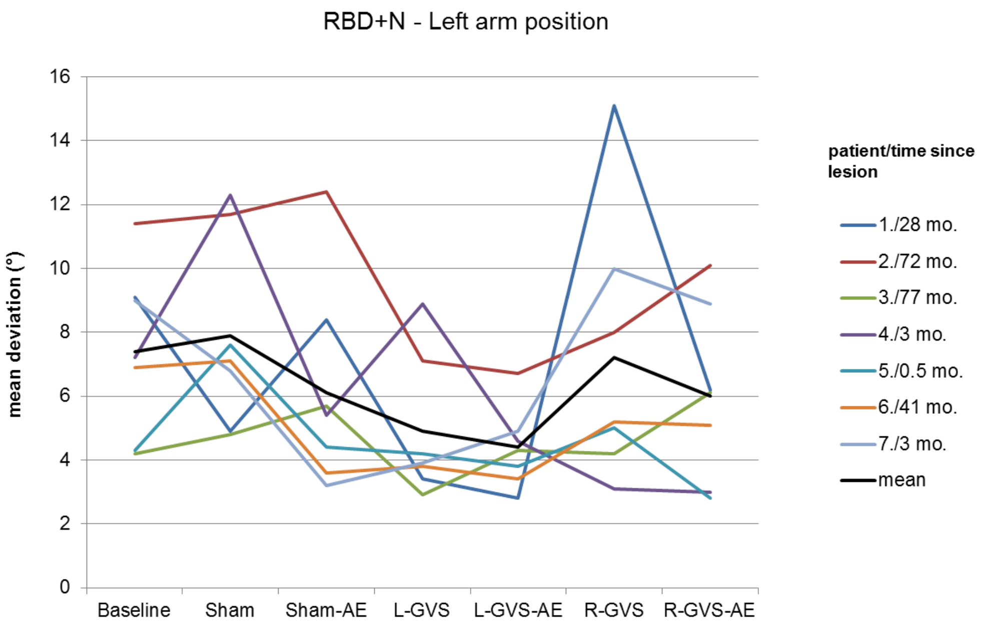


Figure 8 *Individual unsigned errors (in degrees, averaged over 12 trials) of the seven patients with neglect (RBD+N-group) in arm position sense across the different experimental conditions for the left arm and in relation to lesion chronicity (months). Abbreviations: L-GVS: left-cathodal/right-anodal GVS; R-GVS: right-cathodal/left-anodal GVS; AE: after-effect; mo: months. For patient codes and lesion chronicity, see Table 1.*

There were no significant correlations between the clinical characteristics of patients with neglect and the modulation of APS by GVS (Pearson/Spearman: smallest p = .101/.258, largest r_p/r_s = .36/.25). Notably, the exception was a significant positive correlation between deficits in left APS and visual neglect severity (Pearson: r_p = .49, p = .022; Spearman: r_s = .47, p = .027), which was not found for the right arm (Pearson: r_p = .19, p = .407; Spearman: r_s = .09, p = .685).

3.5 Discussion

The present study showed the following results: (i) APS of the left (contralesional) but not the right arm was significantly impaired in our mostly chronic RBD+N patients as compared to RBD-N patients and healthy control subjects. (ii) L-GVS selectively improved the accuracy of APS in RBD+N patients *during* stimulation (significant online-effect). Moreover, the left APS in these patients continued to ameliorate for at least 20 minutes after the end of stimulation (significant after-effect). This improvement was independent from patient characteristics and lesion chronicity (iii) R-GVS significantly worsened APS for the left arm in healthy subjects.

Contralesional arm position deficit in spatial neglect

Consistent with studies in acute patients with neglect (Vallar et al., 1993a) we found a clear *contralateral* but no ipsilateral deficit in APS in our more chronic patients with neglect. Hence, proprioceptive deficits of the contralateral arm are a persistent problem in neglect which correlate significantly with the severity of the syndrome. Despite these minor differences (with respect to the APS deficit in the ipsilesional arm in previous studies (Vallar et al., 1993a; Vallar et al., 1995)) our study confirms that neglect is one contributing factor (Vallar et al., 1993a) to this disturbance as the RBD-N-group performed at the same level to our healthy control subjects. Clinically, these findings suggest a nonvisual, neglect-related deficit in patients with visual neglect that impairs the subjective positioning of the contralateral arm in space in the absence of vision (Vallar et al., 2003).

Vestibular modulation of APS

Only L-GVS significantly improved the accuracy of APS for the left arm in neglect: The beneficial effects on the APS were not only observed during online GVS but seemed to increase further significantly by reaching normal performance 20 minutes post-stimulation. All seven participants with hemineglect showed the above pattern (Figure 7, 8), independently of their lesion chronicity (see Figure 8).

According to transformational theories of neglect, vestibular stimulation improves the deficient egocentric reference by providing additional sensory input which in turn may help to correct the position sense of the left arm (Jeannerod & Biguer, 1987; Karnath, 1994b). This facilitatory effect of GVS may rely on the activation of intact structures within this system that are specifically involved in the re-calibration of body and limb position in space (Fink et al., 2003). The greater efficiency of L-GVS versus R-GVS in modulating APS probably results from the asymmetry of the cortical vestibular system (Dieterich et al., 2003). Here, galvanic inhibition of the left vestibular nerve with excitation of the right vestibular nerve (right-cathodal/left-anodal GVS) results in *right* vestibular cortex activation whereas galvanic inhibition of the right vestibular nerve with excitation of the left vestibular nerve (left-cathodal/right-anodal GVS) (Rinalduzzi et al., 2011) activates vestibular cortices *bilaterally*, at least in healthy subjects (Fink et al., 2003). Thus, it is conceivable that L-GVS leads to a more widespread cerebral activation in *both* hemispheres which could partially compensate for the effects of the typically large brain lesions (Buxbaum et al., 2004) in patients with left neglect. The continuation of the initial improvement 20 minutes after L-GVS stimulation can be explained by long-term potentiation (LTP), a well-known phenomenon of neuroplasticity induced by direct current stimulation (Utz et al., 2010).

Importantly, neither R-GVS nor Sham-GVS influenced APS, thereby ruling out placebo or unspecific repetition effects as confounding factors of the observed improvements. Moreover, the observed modulating effects are unlikely to result from mere attentional cueing towards the stimulating electrode since the subjects could neither feel the stimulation nor discriminate between the different experimental conditions.

The lack of any GVS effect in the patients without neglect concurs with findings showing that sensory stimulation manoeuvres such as GVS or optokinetic stimulation typically do not modulate performance in these patients, probably because their egocentric reference system is unimpaired (Vallar et al., 1993a).

Unexpectedly, R-GVS deteriorated left APS in healthy subjects. This is probably due to R-GVS activating the right (intact) vestibular cortex, which may interfere with regular, intact vestibular activity due to overexcitation in these cortical areas. This, in turn, may induce a temporary disturbance of spatial reference frames, similar to but less pronounced than in neglect (Fink et al., 2003). Comparable disruptive effects of vestibular stimulation on cognitive processes in healthy individuals were observed for spatial memory tasks (Dilda, MacDougall, Curthoys, & Moore, 2012) and tactile exploration (Karnath, Himmelbach, & Perenin, 2003) suggesting that egocentric frames of reference - even though not lesioned - are susceptible to GVS. The lack of a disturbing effect of R-GVS in our RBD-N subjects can be explained by lesion size effects which generally reduce the influence of GVS (Sparing et al., 2009).

Some limitations of our study have to be considered: The sample of patients with neglect was small, requiring replication in larger groups. Moreover, because safety standards for GVS limit exposure to 20 minutes, the number of tests and trials possible in one session are restricted. Finally, the deterioration of left APS in healthy subjects requires further verification in a larger sample.

3.6 Summary

APS for the contralesional arm is impaired in patients with left neglect and improves transiently into the normal range after 20 min of GVS. Therefore, GVS could be a useful add-on-therapy augmenting the effects of other treatments (i.e. limb activation (Reinhart et al., 2012), prism exposure (Dijkerman et al., 2004), feedback training (Carey, 1995)) by ameliorating proprioceptive and other body-related disorders in neglect (Carey, Matyas, & Oke, 1993), as recently observed in a case study of repetitive GVS (Volkening & Keller, 2012).

4 Study 2: Differential effects of galvanic vestibular stimulation on arm position sense in right- vs. left-handers

Schmidt, L., Artinger, F., Stumpf, O., & Kerkhoff, G. (2013). *Neuropsychologia, 51,* 893-899.

4.1 Abstract

The human brain is organized asymmetrically in two hemispheres with different functional specializations. Left- and right-handers differ in many functional capacities and their anatomical representations. Right-handers often show a stronger functional lateralization than left-handers, the latter showing a more bilateral, symmetrical brain organization. Recent functional imaging evidence shows a different lateralization of the cortical vestibular system towards the side of the preferred hand in left- versus right-handers as well. Since the vestibular system is involved in somatosensory processing and the coding of body position, vestibular stimulation should affect such capacities differentially in left- versus right-handers. In the present, sham-stimulation-controlled study we explored this hypothesis by studying the effects of GVS on proprioception in both forearms in left- and right-handers. Horizontal APS was measured with an opto-electronic device. Second, the polarity-specific online- and after-effects of subsensory, bipolar GVS on APS were investigated in different sessions separately for both forearms. At baseline, both groups did not differ in their unsigned errors for both arms. However, right-handers showed significant directional errors in APS of both arms towards their own body. Right-cathodal/left-anodal GVS, resulting in right vestibular cortex activation, significantly deteriorated left APS in right-handers, but had no detectable effect on APS in left-handers in either arm. These findings are compatible with a right hemisphere dominance for vestibular functions in right-handers and a differential vestibular organization in left-handers that compensates for the disturbing effects of GVS on APS. Moreover, our results show superior arm proprioception in left-handers in both forearms.

4.2 Introduction

The human brain is characterized by an asymmetrical organization, consisting of two hemispheres with different functional specializations. For many years, researchers have used handedness as an indirect indicator of cerebral specialization (Amunts et al., 1996; Linkenauger et al., 2009a; Witelson, 1989).

Lateralization of sensory-motor functions in left- vs. right-handers

In general, motor functions are probably more strongly lateralized than emotional, cognitive or sensory abilities (Gutwinski et al., 2011). Moreover, right-handed individuals rely more on their dominant, right hand as compared to left-handers who rely more on both hands (Gonzales, Whitwell, Morrissey, Ganel, & Goodale, 2007; Linkenauger, Witt, Stefanucci, Bakdash, & Proffitt, 2009b). In line with this, cortical representations of the right arm and hand are greater in the left hemisphere of right-handers, whereas left-handers represent these body parts in a more symmetrical fashion in both hemispheres (Linkenauger et al., 2009a). While right-handers show a left-hand advantage for global judgments and a right-hand advantage for local judgments in haptic processing, left-handers exhibit a weaker asymmetry in such bimanual tasks (Tomlinson, Davis, Morgan, & Bracewell, 2011). Gardner and Potts (2010) showed that hand dominance also influences the performance in an own body transformation task. They found an attentional bias toward the side of the observed body that corresponds to the dominant hand of the participants, suggesting a modulatory effect by handedness even in imagined perspective transformations. Hach and Schütz-Bosbach (2010) found evidence for handedness differences in the implicit but not explicit representation of body space and the authors interpreted this result by a greater lateralization in dextrals.

Structural and functional imaging studies corroborate these behavioral results in showing a different organization of the left/right central sulcus (Amunts et al., 1996), the somatosensory cortex (Buchner, Ludwig, Waberski, Wilmes, & Ferbert, 1995), and the parietal lobe (Devlin et al., 2002; Perenin & Vighetto, 1988) in right- vs. left-handers. In a fMRI study concerning hemispheric specialization for praxis, Vingerhoets et al. (2012) found similar lateralized activation patterns for pantomiming learned movements in left- and right-handers but a reduced strength of asymmetries predominantly in the posterior parietal cortex in left-handers. In sum, previous studies suggest stronger structural and functional asymmetries in right-handers as compared to left-handers who show a more symmetrical organization resulting in less asymmetry in sensorimotor tasks performed with the left or right hand.

Cortical vestibular system

The vestibular system is involved in mental timing (Binetti, Siegler, Bueti, & Doricchi, 2012), the recognition of the own body position in space as well the determination of movement in space (Dieterich, 2006), in somatosensory processes (Dijkerman & De Haan, 2007; Ferrè, Sedda, Gandola, & Bottini, 2011; Vallar et al., 1993b) and motor functions (Rode et al., 1998a; Rode et al., 2012). It acts as a basic reference system for the other sensory systems, provides information about spatial orientation and operates in egocentric and allocentric reference frames (Eickhoff et al., 2006). The vestibular system entails a highly organized thalamocortical projection (for a review, see Lopez & Blanke, 2011). Functional imaging studies of the vestibular system using GVS (Bense et al., 2001; Lobel et al., 1998) or CVS (Bottini et al., 1994) have revealed a network of vestibular areas including the temporal, parietal and insular cortices, as well as the putamen and thalamus, which is distributed in both cerebral hemispheres, but with a right-hemispheric dominance in right-handers (Bense et al., 2001; Brandt & Dieterich, 1999; Suzuki et al., 2001). Recent studies complement these findings by showing that vestibular activations in right- and left-handers are stronger in the hemisphere ipsilateral to the preferred hand (Janzen et al., 2008) and showing that vestibular stimulation is based on opioid neurotransmission which is pronounced in the right hemisphere in right-handers (Baier et al., 2010).

Few studies have so far investigated the vestibular network in left-handers. In a PET study of Dieterich et al. (2003), the effects of CVS on vestibular activation in 12 right-handed and 12 left-handed individuals were investigated. In both handedness groups they found significant activations in both hemispheres, both subcortically in the putamen, thalamus and midbrain, as well as cortically in frontal and temporo-parietal areas and the posterior insula. These activations were bilateral, but with a preponderance of the non-dominant hemisphere: in right-handers the right hemisphere, in left-handers the left hemisphere was stronger activated. Dieterich et al. (2003) concluded that cortical and subcortical activations induced by CVS depend on handedness. In their view, vestibular lateralization determines right- or left-handedness, because the vestibular system matures earlier during ontogeny while handedness and language lateralization occur later (Dieterich et al., 2003). There is also evidence that prenatal asymmetry of the vestibular development, among others, may influence handedness and cerebral lateralization because left-otolithic dominance may induce right-sided motoric dominance and a right hemisphere specialization for visuospatial functions (for a general review, see Previc, 1991).

Arm position sense

Proprioception or limb position sense is an important capacity to locate one's own limbs without visual feedback. Impaired position sense leads to imprecise motor functions, reduced spontaneous use of arms, awkward limb positions, reduced safety and postural instability (Dijkerman & De Haan, 2007). Disturbed limb position sense in space or in relation to their own body is frequent in patients with stroke, e.g. of the arm, the APS (Schmidt et al., 2013a; Vallar et al., 1993a; Vallar et al., 1995). Moreover, contralateral APS disorders were more frequent and severe in right brain-damaged patients, especially those with left neglect (Pizzamiglio et al., 1990; Schmidt et al., 2013a; Sterzi et al., 1993; Vallar et al., 1993a; Vallar et al., 1995). Furthermore, there is a close relationship between vestibular cortical projections and hand/arm representations in the central sulcus (Robertson, Tegnerér, Goodrich, & Wilson, 1994).

Rationale of the present study

In light of the abovementioned greater behavioral and anatomical asymmetries in right- vs. left-handers and their differential vestibular brain organization one might expect behavioral asymmetries in APS of the two forearms in left- and right-handers, as shown for other sensorimotor tasks. Moreover, both handedness groups should respond differentially to vestibular stimulation when performing APS. As the cortical vestibular system is dominantly organized in the right parieto-temporal cortex in right-handers (see above), and right-cathodal/left-anodal GVS (R-GVS) leads to an activation of the right vestibular cortex (Fink et al., 2003) this GVS condition should have differential effects on arm position sense in right- and left-handers. In a previous study, we found, as an unexpected side effect, that R-GVS disrupts left APS in right-handers (Schmidt et al., 2013a). Therefore, we expected in the present study, that R-GVS should disrupt left APS in right-handers, but should have no or less disruptive effects in left-handers. In contrast, left-cathodal/right-anodal GVS (L-GVS) might disrupt right APS in left-handers, because of their dominant organization of the vestibular system in the left hemisphere. Alternatively, GVS should have no disturbing effect on APS in left-handers at all, because of their more pronounced *bilateral* vestibular organization.

The present study, therefore, aimed to study the handedness-specific hemispheric lateralization of vestibular functions, with the following questions and hypotheses:

(i) Does APS accuracy of left- and right-handers differ, respectively in the left and right arm, as shown for other motor tasks? We expected that left-handers are more accurate in the APS of *both* arms, whereas right-handers should show a greater right-left asymmetry (see Introduction).

(ii) Does GVS modulate the APS in healthy left-handers in a similar way as shown for right-handers (Schmidt et al., 2013a)? We hypothesized that GVS either has no or only a weak influence on the APS of left-handers due to the missing right hemisphere dominance and/or the greater bilateral organization of the vestibular system in this group.

(iii) Are there polarity-specific effects of GVS on APS? We anticipated no polarity-specific GVS effects in left-handers because the bilateral vestibular organization should compensate the disturbing effects of GVS on APS. In contrast, R-GVS should disrupt left APS in right-handers.

4.3 Methods

Participants

Twelve dominantly left-handed (six females) and 12 dominantly right-handed (four females) neurological healthy individuals, according to the results of a handedness questionnaire (see *Handedness and grip strength assessment*, below), participated in our study (Table 2). Both handedness samples did not differ significantly with respect to age (Mann-Whitney U test: U = 66.5; z = -.32; p = .75), visual acuity (U = 63.5; z = -.51; p = .607), years of education (U = 69.5; z = -.15; p = .879) and gender distribution (Chi-Square test: χ^2 (df=1) = .69; p = .408). All subjects had at least 0.63 (63%) visual acuity for the near viewing distance in order to accomplish proper vision of the target LED during the measurement of the APS (see *Arm position device*, below). The participants gave their written informed consent prior to the examination in accordance with the Declaration of Helsinki II.

Table 2 *Demographic data of the 12 right-handers and 12 left-handers. Abbreviations: Handedness: +100: extreme right-handedness, 0: ambidexter, -100: extreme left-handedness; Visual acuity: binocular, decimal letter acuity for the near viewing distance (0.4 m; 1.0=100%=20/20 Snellen equivalent); n.s.: not significant with $p > .05$.*

	Left-handers (n = 12)	Right-handers (n = 12)	Statistical comparison
Age			p > .05, n.s.
Mean (SD)	59.7 (5.7)	59.4 (6.9)	
Range	51-67	51-71	
Years of education			p > .05, n.s.
Mean (SD)	10.4 (1.4)	10.5 (1.7)	
Range	9-13	9-13	
Gender ratio (male:female)	6:6	8:4	p > .05, n.s.
Handedness			p < .001
Mean (SD)	-91.4 (15.5)	+100 (0.0)	
Range	-100- (-64)	+100-100	
Grip strength			p > .05, n.s.
Left arm (kg)			
Mean (SD)	31.3 (13.2)	25.5 (7.7)	
Range	15-52	20-31	
Right arm (kg)			p > .05, n.s.
Mean (SD)	30.1 (13.4)	32.5 (7.7)	
Range	14-47	27-38	
Visual acuity			p > .05, n.s.
Mean (SD)	0.98 (0.25)	0.93 (0.21)	
Range	0.63-1.25	0.63-1.25	

Handedness and grip strength assessment

Handedness was assessed using the forced-choice hand preference questionnaire by Annett (Salmaso & Longoni, 1985). This ask the participants to indicate the hand he/she usually use to carry out 10 unimanual everyday actions (throw, separate with scissors, comb, use toothbrush, use knife, use spoon, hammer, use screwdriver, strike match, thread) which yields a laterality quotient that ranges from -100 (totally left-handed) to +100 (totally right-handed). A cut-off score of ≤ -60 on this questionnaire was used to classify the individuals as left-handers and a score of ≥ +60 as right-handers. Intermediate scores indicated mixed-handers. According to this classification criterion all participants were clearly attributed as either dominantly left- or right-handed (see Table 2 for further details).

The grip strength of each hand was measured by Jamar hand grip dynamometer (Degasport, D-83115 Neubeuern, Germany). All participants were instructed to hold the arm at a 90° angle beside their body. The grip strength was measured in kilogram per arm, three trials for each hand were performed and averaged subsequently.

Arm position device

The experimental task was an arm position task in order to measure left and right arm APS in the horizontal plane. The used opto-electronic apparatus (Schmidt et al., 2013a) consisted of an arm rest that was movable on a 90° circuit in order to determine the subject´s actual horizontal arm position with a resolution of 1°. A small, manually shiftable, red LED lamp was applied above the arm rest arrangement, likewise movable on a 90° circuit for optical indication of the required arm position. A control panel stored the deviation in degrees of the subjects´ actual arm position from the optically target position. Participants were seated directly in front of the apparatus, easily allowing a comfortable 90° movement of each arm (Figure 9 B). While the investigator moved the subject´s left or right arm slowly (average velocity: 4.3°/s) to the intended position under the LED, the subjects had to indicate verbally when their forefinger was exactly positioned under the LED. All testing took place in complete darkness (~ 1 Lux background illumination) and with a black cape covering the arm and shoulder of the individuals to remove any visual reference cues. Four different starting position (90° = straight ahead, 60°, 30°, 0°) and two different target positions (30°, 60°) were investigated with three trials per position, resulting in a total of 12 trials per forearm. Trials were performed in random order to control for sequence effects (see Figure 9 B).

Two final parameters were computed, separately for each subject, arm and experimental condition. First, unsigned errors (UE) were calculated as absolute deviations from the correct position irrespective of their direction. UE designate the difference between the actual arm position and the target (LED) position (in °) and were averaged over the 12 trials per condition. Second, constant errors (CE) were computed which represent the magnitude *and* direction of the indicated arm position from the target (LED) position (in °, averaged over the 12 trials per condition) Positive constant errors denote deviations away from the subject´s body, negative values indicated a deviation in APS towards the persons´ body.

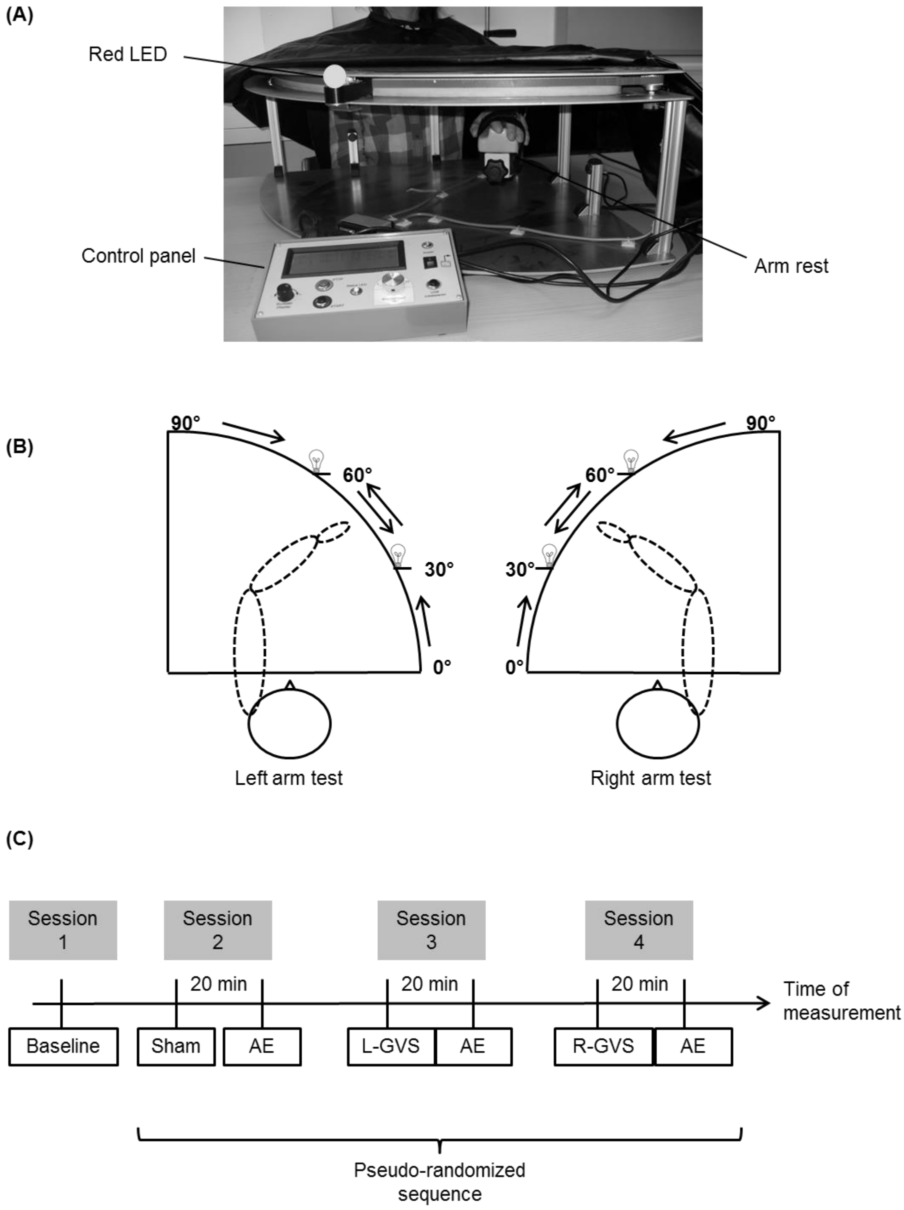


Figure 9 (A) *Layout of the arm position device (APD; see text for details).* ***(B)*** *Schematic view of the APD and of the subject´s position when the left (left part of the figure) or right (right part of the figure) forearm was tested - two different angle positions (30° and 60°) from four different starting positions: 90° (straight ahead), 60°, 30°, 0° are shown.* ***(C)*** *Design of the study with the four different experimental sessions. L-GVS: left-cathodal/right-anodal GVS; R-GVS: right-cathodal/left-anodal; AE: after-effect.*

Galvanic vestibular stimulation

Bilateral bipolar GVS was delivered by a constant current generator that was conducted with a 9-voltage battery (ED 2011, DKI GmbH, D-01277, Germany). GVS was performed by placing two carbon electrodes (50 x 35 mm; anode and cathode) over both mastoids behind the ears with the aid of gauze bandages and leucoplast. These electrodes were embedded in saline-soaked sponges in order to minimize cutaneous sensations and to improve conductivity. Each person underwent three GVS conditions. The polarity of the applied electric currents was changed between the different experimental stimulation conditions. In the L-GVS condition the cathode electrode was placed over the left mastoid and the anode electrode over the right mastoid. In the R-GVS condition this electrode adjustment was inverted. In the Sham condition the two electrodes were attached behind the ears, likewise in the L-GVS condition, but no electric current circulated. In order to prevent any potential cueing effects by the stimulation, we stimulated below the sensation threshold (subliminal). The individual threshold was determined by slowly increasing current intensity in steps of 0.1 mA until the subjects reported slightly tingling underneath the electrodes. All participants reported it underneath the anode. Current was ramped down until the cutaneous sensation stopped. This procedure was repeated twice and the current intensity 0.1 mA below the amplitude at which the patient indicated a tingling was determined as individual threshold. The mean current intensity was 0.7 mA (range: 0.5 - 1.0 mA) for the entire sample and did not differ between the two handedness groups (mean intensity left-handers: 0.7 mA, mean intensity right-handers: 0.7 mA, $U = 54$; $z = -1.06$; $p = .29$). Each experimental session lasted no more than 20 minutes to comply with safety criteria for GVS (Utz et al., 2010). After each GVS session the subjects completed a 34-items questionnaire including possible adverse effects during and after stimulation (Utz et al., 2011b), but neither the left-handers nor the right-handers reported any adverse side-effects.

Procedures

All participants attended four experimental sessions with a between-session-interval of at least 48 hours to prevent potential carry-over effects. The first session included the assessment of demographic data, handedness and grip strength as well as of the Baseline values in the horizontal APS of both arms. In the following three sessions, subjects performed the arm position task while receiving either L-GVS, R-GVS or Sham-GVS in a pseudo-randomized order to avoid potential sequence effects. Moreover, subjects were not aware of the stimulation received, because it was below their perceptual threshold. In order to investigate online- as well as *after*-effects, the electrodes were put off after every 20-minutes-interval of stimulation (respectively Sham stimulation) and the subjects rested in the dark room for 20 minutes. After this break, APS was measured for the second time (named after-effect, AE) without GVS (see Figure 9 C).

Data analysis

All statistical analyses were calculated with SPSS, version 19, and were carried out, separately for the left and right forearm as well as for the two outcome parameters. The data in both samples (left- and right-handers) were severely skewed and therefore not normally distributed (K-S tests: $p \leq .20$), so that the assumptions for ANOVAs were not met. Consequently, non-parametric statistics were used for the analyses. Mann-Whitney U tests were conducted to test for differences in APS between left- and right-handers. Friedman tests were computed to test for differences between the different experimental conditions in the unsigned and constant errors within each handedness groups. Subsequent paired comparisons were run with two-tailed Wilcoxon tests. In addition, one sample t-tests were computed for the constant errors of each handedness group to determine whether they differed significantly from zero. The alpha-level was set at .05 for all analyses.[1]

4.4 Results

Differences between left- and right-handers

Unsigned errors (UE)

The analysis of the UE of the *left* arm did not show a statistically significant difference between the two handedness groups across the GVS conditions (Mann-Whitney U tests: Baseline: $U = 68.5$; $z = -.20$; $p = .840$; Sham: $U = 62$; $z = -.25$; $p = .805$; Sham-AE: $U = 48$; $z = -1.11$; $p = .268$; L-GVS: $U = 46$; $z = -1.50$; $p = .133$; L-GVS-AE: $U = 61$; $z = -.64$; $p = .525$; R-GVS: $U = 43$; $z = -1.67$; $p = .094$; R-GVS-AE: $U = 62$; $z = -.58$; $p = .564$, see Figure 10 A).

In contrast, the analysis of the UE in *right* APS yielded significant differences between the groups during L-GVS-AE ($U = 37.5$; $z = -1.99$; $p = .046$), suggesting greater absolute deviations in the left-handed group as compared to right-handers. In the other conditions, no significant differences between left- and right-handers were found (Baseline: $U = 40.5$; $z = -1.81$; $p = .069$; Sham: $U = 52$; $z = -.86$; $p = .389$; Sham-AE: $U = 43$; $z = -1.42$; $p = .157$; L-GVS: $U = 45$; $z = -1.56$; $p = .119$; R-GVS: $U = 57.5$; $z = -.84$; $p = .402$; R-GVS-AE: $U = 57.5$; $z = -.84$; $p = .402$, see Figure 10 B).

[1] Specific a-priori hypotheses were defined prior to the experiments (see *Rationale of the present study*).

Constant errors (CE)

The analysis of the CE in *left* APS revealed significantly different results between left- and right-handers under the Sham-AE ($U = 27$; $z = -2.40$; $p = .016$) and R-GVS-AE condition ($U = 33$; $z = -2.25$; $p = .024$). There were no further significant differences between the handedness groups in any of the other experimental conditions (Baseline: $U = 52.5$; $z = -1.13$; $p = .260$; Sham: $U = 40$; $z = -1.60$; $p = .109$; L-GVS: $U = 51$; $z = -1.21$; $p = .225$; L-GVS-AE: $U = 50.5$; $z = -1.24$; $p = .214$; R-GVS: $U = 50$; $z = -1.27$; $p = .204$, see Figure 11 A).

Furthermore, no significant differences between left- and right-handers were found for the CE in *right* APS in any of the GVS conditions (Baseline: $U = 45$; $z = -1.56$; $p = .119$; Sham: $U = 64$; $z = -.12$; $p = .902$; Sham-AE: $U = 45.5$; $z = -1.26$; $p = .207$; L-GVS: $U = 63.5$; $z = -.49$; $p = .623$; L-GVS-AE: $U = 58$; $z = -.81$; $p = .418$; R-GVS: $U = 57.5$; $z = -.84$; $p = .402$; R-GVS-AE: $U = 47$; $z = -1.44$; $p = .149$, see Figure 11 B).

Effects of GVS on APS in the two handedness groups

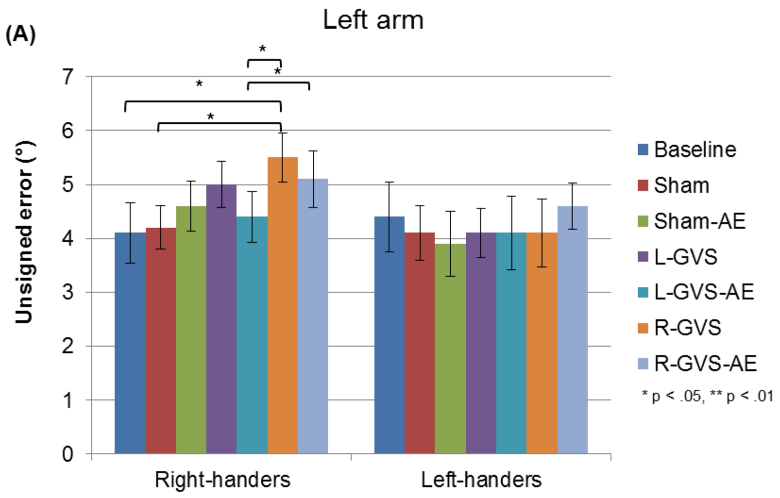
Unsigned errors

Significant differences were found between the seven experimental conditions only in the *left* arm of the right-handed group (Friedman test: χ^2 (df=6, N=12) = 14.03; $p = .029$). There were no significant differences neither for the right arm in right-handers (χ^2 (df=6, N=12) = 8.97; $p = .175$) nor for the left-handed group in the left (χ^2 (df=6, N=12) = 5.08; $p = .533$) and right arm (χ^2 (df=6, N=12) = 3.36; $p = .762$). Subsequent paired comparisons of left arm scores in the right-handers revealed that the UE during R-GVS were significantly greater than those at Baseline (Wilcoxon test: $z = -2.31$; $p = .021$), Sham ($z = -2.04$; $p = .041$) and L-GVS-AE condition ($z = -2.00$; $p = .045$.). Moreover, right-handers showed greater unsigned deviations in the right arm in the R-GVS-AE condition as compared to the L-GVS-AE condition ($z = -2.04$; $p = .041$, see Figure 10 A, B).

Constant errors

As reported for unsigned errors, there were significant differences between the different GVS conditions only in the *left* arm of the right-handers (χ^2 (df=6, N=12, = 12.97; $p = .044$). Right arm scores of the right-handers (χ^2 (df=6, N=12) = 4.89; $p = .558$) as well as both arm conditions in the left-handed group (left arm: χ^2 (df=6, N=12) = 4.98; $p = .546$; right arm: χ^2 (df=6, N=12) = 10.58; $p = .102$) yielded no significant differences across the experimental conditions. Subsequent paired comparisons in the right-handed group indicated that the left APS deteriorated significantly during R-GVS as compared to Baseline ($z = -2.43$; $p = .015$) and to L-GVS ($z = -2.04$; $p = .041$). Furthermore, right-handers showed a significant deterioration in left APS under the R-GVS-AE condition as compared to Baseline ($z = -2.05$;

p = .041). Note that both groups showed almost exclusively negative deviations in both arms, but more pronounced in the right-handers. This indicates a systematic bias in APS towards the subject`s own body (see Figure 11 A, B and *Additional analyses*, below).



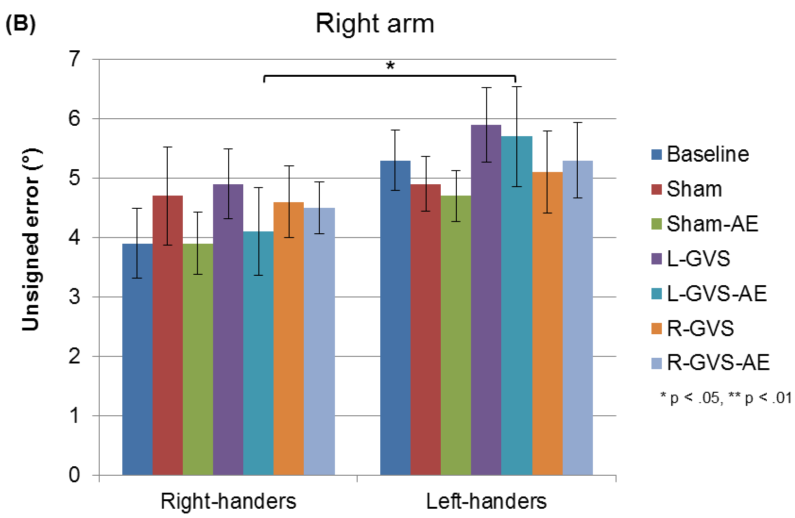


***Figure 10** Mean unsigned errors (in degrees) and standard error of the mean (SEM) in the different experimental conditions of the left **(A)** and right arm **(B)**, separately for right- and left-handers. L-GVS: left-cathodal/right-anodal GVS; R-GVS: right-cathodal/left-anodal GVS; AE: after-effect.*

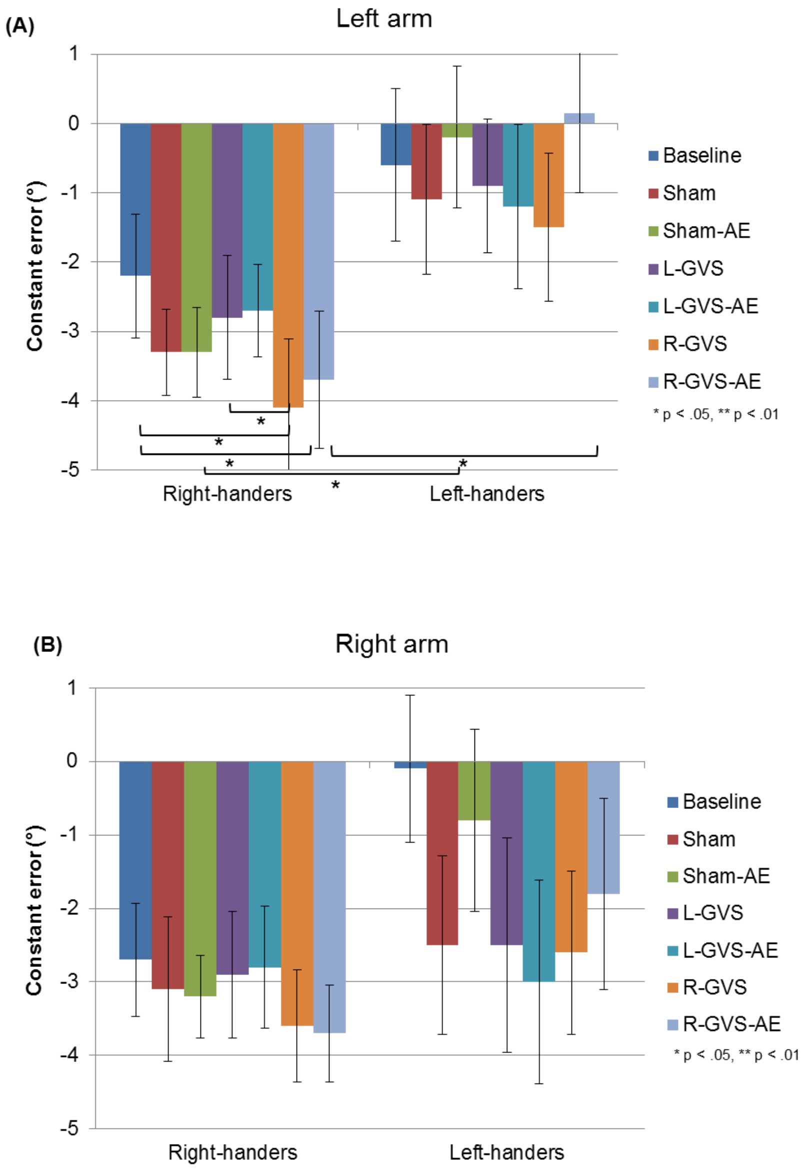


***Figure 11** Mean constant errors (in degrees) and standard error of the mean (SEM) in the different experimental conditions of the left **(A)** and right arm **(B)**, separately for right- and left-handers. L-GVS: left-cathodal/right-anodal GVS; R-GVS: right-cathodal/left-anodal GVS; AE: after-effect.*

Additional analyses

One-sample t-tests against zero showed that constant errors differed significantly from zero only in the right-handed group, both for the right ($T(11) = -3.52$, $p = .005$, $d = -2.72$) and the left arm ($T(11) = -2.48$, $p = .031$, $d = -2.23$), suggesting a significant proximal deviation in APS toward the subject´ body in this group in both arms. In contrast, no significant differences from zero were found either for the right (T(11) = -.11, p = .914, d = -.12) nor the left arm (T(11) = -.55, p = .596, d = -.62) in the left-handed group (see Figure 11 A, B).

In addition, effect sizes (Pearson´s correlation coefficient r_p) for the comparisons (Wilcoxon tests) between the GVS conditions in left APS were computed, separately for left- and right-handers, in order to affirm that the disturbing effect of GVS is smaller on left- than on right-handers. These values, separately for the UE and CE, are depicted in Table 3. As can be seen, all values for GVS in right-handers showed large effects (r = .50; Cohen, 1988) in contrast to the effect sizes in left-handers that are at most of a small or medium extent (r_p < .50).

Table 3 *Effect sizes (Pearson´s correlation coefficients r_p) for the significant comparisons (Wilcoxon tests) between the GVS conditions in left APS, separately for left- and right-handers and for unsigned and constant errors. Abbreviations: UE: unsigned errors; CE: constant errors. R-GVS: right-cathodal/left-anodal; L-GVS: left-cathodal/right-anodal; AE: after-effect.*

		Left-handers	Right-handers
UE	Baseline vs. R-GVS	.09	.67
	Sham vs. R-GVS	.09	.59
	R-GVS vs. L-GVS-AE	.10	.58
	R-GVS-AE vs. L-GVS-AE	.27	.59
CE	Baseline vs. R-GVS	.36	.70
	Baseline vs. R-GVS-AE	.37	.59
	R-GVS vs. L-GVS	.32	.59

4.5 Discussion

The aims of the present study were to investigate whether (i) left and right APS differ between left- and right-handers (ii) GVS has a different, modulatory effect in healthy left- and right-handers (iii) this effect is polarity-specific. Below, we discuss the obtained results in detail.

Differences in arm position sense in left- versus right-handers

First, we did not find significant differences in the Baseline APS in both arms between the two handedness groups. However, right-handers showed a significant direction-specific bias in both forearms in Baseline APS, whereas left-handers did not have a significant deviation in any arm (see Figure 11 A, B). This points to an overall greater accuracy of APS in left-handers for both arms as compared to right-handers with respect to constant errors in this task. Put differently, left-handers perform better than right-handers in body-related cognition. This finding neatly fits with recent studies reporting greater behavioral (e.g. Hach & Schütz-Bosbach, 2010; Laeng & Peters, 1995; Linkenauger et al., 2009a) as well as neuroanatomical symmetries (Amunts et al., 1996; Hécaen, De Agostini, & Monzon-Montes, 1981; Vingerhoets et al., 2012) in body or motor representations in sinistrals. This can be explained by the fact that left-handers are rather flexible in their hand use and frequently shift to the right hand, if necessary (Bryden, 1982). Moreover, sinistrals may pay more attention on correct perception and positioning of their body parts, e.g. the left or right forearm, due to the forced adaptation to "living in a right-handed world". Our finding that right-handers showed significant APS errors in *both* forearms differs from results reported in previous studies (Gonzales et al., 2007; Linkenauger et al., 2009a) who found that right-handers show a strong right-left asymmetry in limb-related tasks, hence better performance in their right, dominant limb as compared to the left one. This difference may be related to task differences. Moreover, the finding that our left- and right-handers showed similar unsigned errors in APS but differed in their constant errors in the Baseline condition speaks in favor of a direction-specific shift toward the own body serving as an important spatial reference in proprioception in right-handers. This finding replicates earlier studies on APS using a different measurement technique (Vallar et al., 1993a; Vallar et al., 1995) who also reported errors in APS towards the own body in right-handers. Obviously, right-handers rely more strongly on their own body as a reference frame in near space to determine the position of their limbs in space.

Vestibular disruption of arm position sense in dextrals

The present data show - to our knowledge for the first time - that R-GVS perturbs APS in the left arm of healthy right-handers. This transient disruption of normal limb position coding can be explained by the fact that R-GVS activates the right vestibular cortex unilaterally in right-handers whereas L-GVS induces bilateral vestibular activation (Rinalduzzi et al., 2011; Vallar et al., 1993b). Due to the anatomical asymmetry of the vestibular system in right-handers (Dieterich et al., 2003), R-GVS leads to a focal cerebral overexcitation in the right hemisphere and, thereby, induces an interference with, otherwise, normal vestibular activity important for arm positioning in right-handers. Thus, GVS perturbs human brain function temporarily by inducing a disturbance of the spatial reference frame (Fink et al., 2003). Similar disturbing effects of vestibular stimulation on cognitive processes have been observed in spatial memory tasks (Dilda et al., 2012), tactile exploration (Karnath et al., 2003) or line bisection judgments (Fink et al., 2003) in healthy subjects. These findings are in accordance with other results of brain stimulation techniques which are used as "virtual lesion techniques", such as tDCS and TMS and their effects on a variety of cognitive and motor functions (Sparing & Mottaghy, 2008).

Implications and limitations

In contrast to the well-studied effects of GVS in right-handers, little is known about their effects in left-handers. In the present study, subliminal GVS had no effect on APS in left-handers, under no stimulation condition. Therefore, we found a significant difference for the CE of left APS under R-GVS-AE between the two handedness groups. This finding can be well explained by the hypothesis of a reduced vestibular lateralization in left-handers as compared to right-handers, as shown for many cognitive/motor abilities (for a review, see Gutwinski et al., 2011). It seems plausible to assume that the differential organization of the cortical vestibular system in left-handers allows to compensate for the perturbing effects of R-GVS on APS which we observed in our dextrals.

Alternatively, the cortical vestibular system of left-handers shows a mirror-symmetric organization to that of right-handers, which implies a left hemisphere dominance according to the recent results of Dieterich et al. (2003) and Janzen et al. (2008). This result is at variance with our findings in left-handers, because according to this view L-GVS should have induced a similar disturbing effect on APS in left-handers as R-GVS on APS in right-handers. However, no such effect was observed in our left-handed sample. Thus, our results are easier to reconcile with the hypothesis of less lateralized vestibular system in sinistrals.

Alternatively, it might also be conceived that proprioception of the arm relies on different brain structures in left- as right-handers so that GVS should not necessarily modulate the involved brain structures in left-handers, i.e. because they are remote from those brain structures activated by GVS (see Introduction). This is an empirical question for future research and beyond the scope of the present study. Finally, each handedness group included a rather small sample, requiring replication in a larger sample, in order to reveal the generality of our findings.

4.6 Conclusions

Sinistrals perform superior to dextrals in both forearms when judging their absolute, horizontal arm position in the absence of vision in space. GVS temporarily disrupts this proprioceptive ability of the left arm in dextrals but has no effect in matched sinistrals. This latter result supports the view that the building up and updating of cortical representations of body parts is modulated by incoming vestibular stimulation (Rode et al., 2012), with differential effects in left- versus right-handers.

5 Study 3: Effects of age, sex and arm on the precision of arm position sense – left-arm superiority in healthy right-handers

Schmidt, L., Depper, L., & Kerkhoff, G. (2013). *Frontiers in Human Neuroscience, 7:915*. doi: 10.3389/fnhum.2013.00915

5.1 Abstract

Position sense is an important proprioceptive ability. Disorders of APS often occur after unilateral stroke, and are associated with a negative functional outcome. In the present study we assessed horizontal APS by measuring angular deviations from a visually defined target separately for each arm in a large group of healthy subjects. We analyzed the accuracy and instability of horizontal APS as a function of age, sex and arm. Subjects were required to specify verbally the position of their unseen arm on a 0-90° circuit by comparing the current position with the target position indicated by a LED lamp, while the arm was passively moved by the examiner. Eighty-seven healthy subjects participated in the study, ranging from 20 to 77 years, subdivided into three age groups. The results revealed that APS was not a function of age or sex, but was significantly better in the non-dominant (left) arm in absolute errors (AE) but not in constant errors (CE) across all age groups of right-handed healthy subjects. This indicates a right hemisphere superiority for left arm position sense in right-handers and neatly fits to the more frequent and more severe left-sided body-related deficits in patients with unilateral stroke (i.e. impaired arm position sense in left spatial neglect, somatoparaphrenia) or in individuals with abnormalities of the right cerebral hemisphere. These clinical issues will be discussed.

5.2 Introduction

Proprioception is defined as the sense of position and movement of the limbs without information coming from the visual system (Fuentes & Bastian, 2010). Proprioceptive abilities are essential for orientation and moving in space and engaging with the environment. They are the basis for goal-directed movements of the limbs as well as for locating our limbs without looking and therefore important for nearly all daily life activities (Carey et al., 1996). This includes functions like the control of aiming accuracy, performance of movement sequences, reaching and tracking movements like grasping and manipulating objects as well as the control and correction of ongoing movements. Impairments in proprioception most likely affect any of those abilities and these deficits are frequent, occurring in some 34-64% of stroke patients (Connell, 2008). Proprioceptive deficits cause difficulties and insecurity in many activities of daily living, can compromise personal safety (Carey et al., 1996) and lead to postural instability when e.g. limbs are used to compensate for balance disturbances (Adamo et al., 2007). There is also a relationship between deficits in proprioception in the elderly and sensorimotor dysfunctions, e.g. postural control or balance, and activities of daily living (for a review, see Goble et al., 2009a).

Clinical significance of proprioceptive loss

Loss of limb position occurs in one third to half of stroke patients (Carey, 1995; Shah, 1978; Smith et al., 1983) and mostly affects the contralesional side of the body but can also affect the ipsilesional side (Sartor-Glittenberg & Powers, 1993; Vallar et al., 1993a; Vallar et al., 1995). Patients show disastrous constraints in everyday life as in safety, postural stability and motor functions (Carey, 1995; Carey et al., 1996; Dijkerman & De Haan, 2007) and impaired APS is associated with poorer and longer motor recovery of the hemiparetic or hemiplegic arm (De Weerdt et al., 1987; Feys et al., 2000; Kuffosky et al., 1982; Wade et al., 1983; Wadell et al., 1987). Historically, impaired APS has been considered to have the same incidence after lesions to the right and left hemisphere (Reinhart et al., 2012; Shah, 1978; Vallar et al., 2003). In contrast, recent studies found a strong relationship between APS disorders, lesions to the right hemisphere and left spatial neglect (Pizzamiglio et al., 1990; Schmidt et al., 2013a; Vallar et al., 1993a; Vallar et al., 1995), and that impaired APS occurs more often after right- than left hemisphere lesions (Sterzi et al., 1993). Moreover, there is also a higher incidence of left spatial neglect following right brain lesions versus right neglect after left hemisphere lesions (Azouvi et al., 2002; Beis et al., 2004; Gottesman et al., 2008; Husain, 2008; Kleinman et al., 2007; Suchan et al., 2012). These convergent findings suggest a common underlying mechanism resulting in a higher incidence of both disorders in patients with right hemisphere lesions. Another argument in favor of such a common mechanism is the observation that "bottom-up" treatments of the neglect syndrome based on sensory stimulation such as optokinetic or vestibular stimulation not only improve *visuospatial* neglect symptoms (optokinetic: Kerkhoff et al., 2006; Kerkhoff et al., 2013; Kerkhoff et al., in press; Pizzamiglio et al., 1990; vestibular: Vallar et al., 1993b), but also temporarily reduce the disordered APS in left neglect (optokinetic: Vallar et al., 1993a; Vallar et al., 1995; vestibular: Rode et al., 1992; Rode & Perenin, 1994; Schmidt et al., 2013a). This finding favors the assumption that position sense deficits in spatial neglect have a nonvisual component. This entails the defective perception of the spatial position of body parts (i.e. the contralesional, left arm) due to neglect and an ipsilesional shift in the spatial representation of these body parts and external objects in space. This model of bodily perception (Vallar et al., 1993b) was used to explain the abovementioned findings in patients with neglect. According to this model, incoming sensory (e.g. proprioceptive) information from each side of the body is first processed by each hemisphere, but with a stronger contralateral processing stream. Second, somatotopic representations are entered in an egocentric representation of the body. Interestingly, there is an interhemispheric imbalance with a greater ipsilateral body representation of the right body side and a smaller representation of the left body side. This results in a higher susceptibility of the right cerebral hemisphere for left-sided body-related deficits when lesioned. In summary, in patients with right hemisphere lesions the building-up and updating of the egocentric representation of their body and of the extrapersonal space is perturbed (Vallar et al., 1993a). Due to the assumptions about an asymmetric body representation, this model also explains the asymmetric incidence and why neglect and impaired APS so often are jointly impaired after right brain lesions. Moreover, a right hemisphere dominance in spatial perception, e.g. of limb movements, is also supported by imaging studies (e.g. Naito et al., 2005).

Assessments of position sense

To date, most studies in clinical and healthy populations have examined lower limb position sense, although several studies have also measured position sense of the upper limb (e.g. Carey et al., 1993; Schmidt et al., 2013a; Vallar et al., 1993a; Vallar et al., 1995). Assessment of limb position sense is often conducted by passively moving a single joint to a requested position in the horizontal or vertical plane, while other paradigms require the subject to actively move the limbs towards a target position (Jones, Cressman, & Henriques, 2010). Such experiments investigate the accuracy of "active" limb positioning towards a requested target position, typically in the absence of vision. There are two common paradigms for "active" position sense tasks which vary in their demands on cognitive processing: in "ipsilateral remembered matching tasks" the subject's hand is guided by the examiner to a target position (Goble et al., 2009a). After returning the hand to the starting position, the subject is required to reproduce the target position with the same forearm only supported by his/her proprioceptive memory. These tasks make predominantly demands on the retrieval of memory-based proprioceptive information. In "contralateral concurrent matching tasks" the hand is positioned in a target position but is not being returned to the starting point. Instead, subjects are asked to match the target position with the other hand (Goble et al., 2009a). This kind of tasks requires the interhemispheric transfer of proprioceptive information. "Contralateral remembered matching task" are a combination of the two former ones in which the forearm is returned to the start position and the target position has to be reproduced by matching with the other forearm (Adamo et al., 2007). This latter task poses the highest demands on cognitive abilities during proprioceptive testing, which in turn can influence the former ones, particularly in the elderly (Li & Lindenberger, 2002). Apart from this, those more sophisticated methods also require some basic cognitive capacities (i.e. working memory, cf. Adamo et al., 2007, understanding complex instructions) which are often impaired after acquired brain damage. Evidently, such testing protocols of position sense require different sensory-motor and of course neural mechanisms and assessment methods must take into account the motor and cognitive impairments of patients after stroke (Carey et al., 1996). As a consequence, clinically suitable assessment methods should ideally be simple enough to be applicable in most patients or healthy subjects (Carey et al., 1996), and at the same time sensitive enough to detect even subtle impairments in a limited time.

Most studies of position sense, so far, used paradigms like pointing (Vallar et al., 1993a), reaching (Gordon et al., 1995), matching (Newport et al., 2001; Van Beers et al., 1998) or other judgment tasks (Wilson et al., 2010) to analyze APS in patients and healthy subjects. These methods provide most often ordinal or categorical ratings. Some of them only use a three- (Sterzi et al., 1993) or four-point scale (Vallar et al., 1993a; Vallar et al., 1995) which are discrete scales and deliver only qualitative scores which are often not sensitive to changes after modulation or therapy and are not able to discriminate subtle deficits (Dukelow et al., 2010). Furthermore, some methods lack age- and sex-specific normative data and/or psychometric criteria (i.e. objectivity, reliability; Carey, 1995). Clinicians assess position sense often merely by asking patients to discriminate whether their finger or toe is moved upward or downward by the experimenter (Bickley, 2012; Sterzi et al., 1993), finger finding, positional mimicry or two-point discrimination (Lincoln et al., 1991) as well as by using the thumb localizing task (Hirayama et al., 1999). These clinical assessments also show no or poor psychometric criteria (e.g. interrater reliability), are also not sensitive enough and lack normative data (Carey, 1995; Garraway et al., 1976; Lincoln et al., 1991). However, recent studies show that there are some promising tools available for the quantitative evaluation of sensorimotor functions of upper extremities. For example, robotic devices circumvent the abovementioned limitations of standard clinical assessment scales (for a review, see Scott & Dukelow, 2011). In this context the bilateral robotic exoskeleton called KINARM (Scott, 1999) has to be mentioned that measures horizontal limb position sense e.g. in mirror matching (Dukelow et al., 2010; Fuentes & Bastian, 2010) or reaching tasks (Coderre et al., 2010). Another new method for assessing hand position sense uses a magnetic motion tracking system with sensors attached on each hand in order to record movement trajectories in 3D coordinates (Leibowitz et al., 2008). While such sophisticated methods undoubtedly reveal interesting and novel scientific insights into the spatial and kinematic aspects of proprioceptive tasks, they may also show limitations in their clinical suitability. Hence, such robotic devices may entail the risk of automatic movements without control for patients with motor impairments and reduced flexibility in limbs. Moreover, they are often too complex for everyday clinical practice. Therefore, assessment tools for limb position sense which are easy-to-use, quick to perform, sensitive to changes (i.e. due to therapy) and which have normative values are needed. Carey and colleagues (1996; 2002 for more details) developed such a quantitative measure, termed the Wrist Position Sense Test that meets these afore-mentioned criteria. We adopted their approach to develop a similar test of APS in the horizontal plane, with emphasis on the static, endpoint component of proprioception.

The aims of the present study are threefold: First, we shortly describe this recently developed device for the assessment of horizontal APS of both forearms. Note that we have deliberately chosen a simple and easy-to-use device that is suitable for acute stroke patients, can be performed quickly within the limited time available in the clinical context, and is sensitive enough to detect changes throughout modulation or therapy. Second, we report normative data from 87 healthy subjects in the age range of 20-77 years for both arms and sexes collected with this new device. Third, we analyzed possible laterality, age or sex effects of APS for both arms, as this might offer interesting insights into the hemispheric (a)symmetry of position sense and can be related to impairments of APS in stroke patients. Finally, we discuss our results in relation to clinical findings of disturbed body cognition and awareness (i.e. somatoparaphrenia) in stroke patients and other (pre-)clinical disorders showing disturbed processing or awareness of their own body.

5.3 Methods

Participants

A total of 87 healthy subjects participated in the present study. They were recruited by public bulletins on campus, circular emails and by word of mouth. Inclusion criteria were right-handedness according to the forced-choice hand preference questionnaire by Annett (Salmaso & Longoni, 1985) and visual acuity of at least 0.5 (20/40 snellen equivalent) for the near viewing distance (0.4 m) in order to see the red LED, with all subjects wearing corrective glasses if necessary. Moreover, grip force was measured by Jamar hand grip dynamometer (Degasport, D-83115 Neubeuern, Germany) to rule out a potential influence of hand strength on APS. Participants had to hold their shoulder in 90 degrees of abduction and their elbow in 30 degrees of flexion by the side of their body, grip strength was measured in three trials for each hand and the outcome parameter was the averaged strength in kilogram, separately for each arm (see also Schmidt et al., 2013a). Exclusion criteria were a history of neurological and psychiatric disorders, dementia and physiological impairments of the arm which would not allow arm movements (see Table 4). Subjects were divided into three age groups: 20-40 years old (n = 40; mean age = 27.8; range = 20-40 years; 12 males, young group), 41-60 years old (n = 22; mean age = 52.9; range = 44-58 years; 11 males, mid-aged) and > 60 years old (n = 24; mean age = 67.8; range = 61-77 years; 13 males, old group). The three groups did not differ significantly with respect to sex (χ^2 (df= 2) = 3.97, p = 0.137).

All subjects had at least 1.0 (20/20 snellen equivalent) visual acuity for the near viewing distance and all gave their written consent prior to the examination in accordance with the Declaration of Helsinki II and the local ethical guidelines (Ärztekammer Saarland, Germany).

Table 4 *Demographical and experimental data of the three age groups and total group. Abbreviations: m, male; f, female; handedness/lateralization quotient: +100: extreme right-handedness, 0: ambidexter, -100: extreme left-handedness; visual acuity: binocular, decimal letter acuity for the near viewing distance (0.4m; 1.0 = 100% = 20/20 Snellen equivalent); grip force in kg (see text for further details).*

Age group	N	Mean age (range)	Sex	Handedness/ Mean laterality quotient (range)	Mean visual acuity near (range)	Mean grip force, right arm (range)	Mean grip force, left arm (range)
1 (20-40 years)	40	27.8 (20-40)	12m, 28f	94.13 (40-100)	1.1 (0.8-1.25)	31.2 (16-57)	28.9 (13-57)
2 (41-60 years)	22	52.9 (44-58)	11m, 11f	94.86 (25-100)	1.0 (0.8-1.25)	32.1 (20-63)	30.0 (16-52)
3 (>60 years)	25	67.8 (61-77)	13m, 12f	97.60 (40-100)	1.0 (0.8-1.25)	31.1 (10-55)	28.5 (12-49)
Total	87	49.5	36m, 51f	95.31	1.0	31.4	29.1

Arm Position Device

We developed an opto-electronic device (APD, Figure 12 A-C) specifically for measuring angular forearm displacement of the elbow joint in the horizontal plane. The APD consists of a 0-90° circuit with a small red LED lamp attached to the circuit The LED lamp was manually adjusted by the examiner to set the optically required target position. The subject´s forearm was placed and fixed with palm down on an arm support with the index finger lying extended on a special gap while the other fingers form a fist. This made sure that the tip of the index finger of all subjects (irrespective of individual arm length) was always positioned in the same spatial position relative to the LED. The circuit of the gap on the arm support and the circuit of the LED were perfectly aligned above each other and, therefore, the forearm was not visible for the patient (see Figure 12). The arm support was likewise moveable in the horizontal plane from 0-90° for elbow joint rotation in order to locate individual´s actually horizontal arm position. A digital control panel showed the difference in degrees of visual angle between the optically required position (position of the LED) and the current position of the subject’s forearm (position of the arm support) with a resolution of 0.1° (for further details, see Schmidt et al., 2013a; Schmidt et al., 2013b).

(A)
(B)
(C)

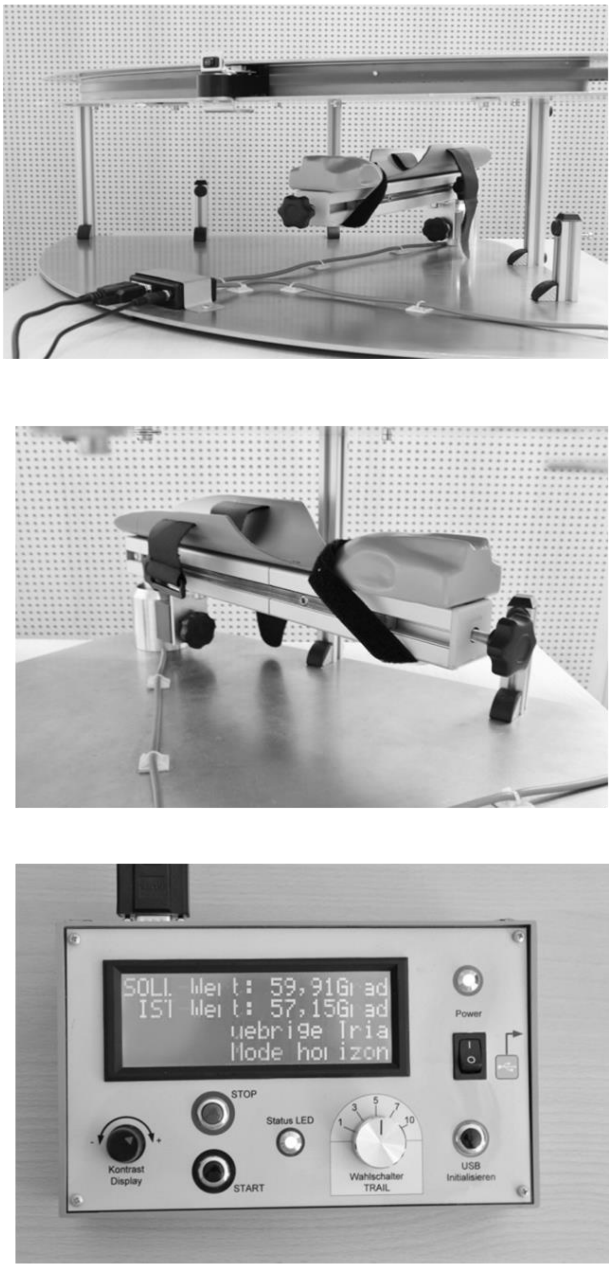


Figure 12 (A) *Layout of the APD (see text for further details).* ***(B)*** *Arm support.* ***(C)*** *Control panel.*

Procedure

During assessment of APS subjects were sitting upright in front of the APD, with either the right or the left arm resting on the arm support (Figure 12). The sequence of the arms tested was pseudo-randomized across subjects. The examiner, sitting in front of the subject, moved the subject's forearm towards the intended position (indicated by the LED lamp) by shifting the arm support with an attached knob in order to enable a constant velocity (average: 4.3

deg/s). Subjects did not actively move their arm to the required position but rather their arm was moved passively by the examiner. Participants were asked to verbally specify the point when their index finger was exactly below the LED lamp. The center of rotation of the device was the elbow joint. The experimenter moved the forearm to two different angle positions of the elbow joint (30° and 60° flexion) from four different starting positions: 90° (forearm completely extended), 60° flexion, 30° flexion, 0° (forearm completely bent), resulting in 30° movements per trial, respectively (Figure 13). Participants performed six trials per LED position, that is three trials +30° (bent movements) and three trials -30° (extended movements) of the true target position (see direction of the black arrows in Figure 13), resulting in 12 trials per arm, which were performed in random order for controlling of sequence effects. Trials were averaged for the analyses, separately for each arm. During measurement the room was darkened (1 Lux illumination) and participants wore a black cape that ensured that the arm that was tested (up to the shoulder) was occluded from vision. Thus, visual cues (i.e. of the arm or the environment) were not available for the subject except the red LED. Participants did not receive any feedback about their performance, nor were there any time constraints for performing the task. Each test session were performed within a maximum of 20 minutes for both arms.

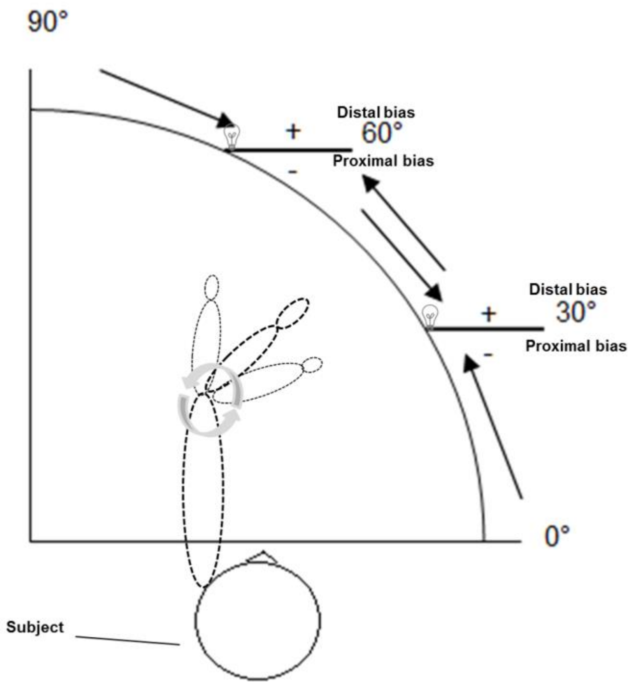


Figure 13 *Schematic drawing of the APD used in the present experiment when the left forearm was tested. Two different angle positions of the elbow joint (30° and 60° flexion) from four different starting positions: 90° (forearm completely extended), 60° flexion, 30° flexion, 0° (forearm completely bent) were tested. Participants performed six trials per LED position, that is three trials +30° (bent movements) and three trials -30° (extended movements) of the true target position (see direction of the arrows). Negative symbols indicate proximal deviations (towards the own body), positive symbols distal deviations (away from the own body) (see text for further details).*

Statistics

Due to the focus on static position sense, rather than kinesthetic movement sense, the final scores were mean deviations of the subject´s actual horizontal arm position from the required LED position (in °), separately for each arm.

First, we calculated the AE, the mean unsigned deviations in degrees from the required target position, irrespective of their direction. Second, the CE were computed as the mean signed deviations from the target position in degrees. Positive values indicate a distal bias (away from the own body), negative values a proximal bias (towards the own body; see positive and negative symbols in Figure 13). This parameter serves as an indicator of accuracy in APS. Third, the interval of uncertainty was determined by subtracting the minimal from the maximal absolute deviation of the 12 trials. This parameter indicates the complete range within which the subject considers the index finger as exactly below the LED lamp. This value was used to calculate the difference threshold or difference limen (DL), defined as one-half of the interval of uncertainty and, thus, serves as an indicator of stability and precision in APS. Analyses of variance with the between factors ‘age group’ (20-40 years, 41-60 years, > 60 years) and ‘sex’ (male, female) and the within factor ‘arm’ (right, left) were carried out, separately for AE, CE and DL with subsequent Bonferroni-adjusted t-tests for multiple comparisons (Holm, 1979). One sample t-tests against zero were run for the CE of each age group, separately for the left and right arm. In addition, two tailed Spearman correlation coefficients were computed for the three outcome parameters between the right and the left arm as well as between grip strength and CE. The alpha-level was set at $p = 0.05$, two-tailed for all analyses.

5.4 Results

Table 5 summarizes the mean results for the AE, CE and DL in APS measured with the APD for both arms and for the three age groups separately. In addition, 95% confidence intervals are indicated, that may be helpful for clinical use.

Table 5 *Summary of the normative data for APS measured with the APD for both arms, separately for the three age groups and the three outcome parameters: mean absolute errors (AE), mean constant errors (CE) and mean difference threshold (difference limen, DL) in degrees. 95%-confidence intervals are indicated. SD: standard deviation.*

	20-40 years			**41-60 years**			**>60 years**		
Right arm									
	AE	CE	DL	AE	CE	DL	AE	CE	DL
Mean (°)	4.68	-.57	.21	4.65	-2.55	.25	4.99	-2.00	.54
SD (°)	1.78	3.71	1.34	1.77	3.31	1.17	2.99	3.40	2.69
Confidence intervals (°)	4.11-5.25	.-1,76-.62	2.66-3.52	3.86-5.44	-4.02-(-1.08)	2.26-3.30	3.77-6.23	-3.41-(-.60)	2.16-4.38
Left arm									
Mean (°)	4.28	-.89	.24	3.89	-1.81	.32	4.23	-1.14	.23
SD (°)	1.76	3.36	1.54	1.72	3.15	1.51	1.68	2.79	1.13
Confidence intervals (°)	3.71-4.84	-1.97-.18	2.20-3.19	3.14-4.66	-3.20-(-.41)	1.95-3.29	3.54-4.93	-2.29-.01	1.98-2.91

Absolute errors

There was a significant main effect for arm ($F(1,81) = 4.02$, $p = 0.048$, $\eta^2 = .042$). Subsequent t-tests showed that AE in the right arm were significantly larger than in the left arm ($T(86) = 2.18$, $p = .032$). The analyses showed no further significant main effect of age group ($F(2,81) = 0.32$, $p = 0.725$, $\eta^2 = .008$) or sex ($F(2, 81) = 0.01$, $p = 0.929$, $\eta^2 = .000$). Factors did not interact significantly with each other (arm × age group: $F(2,81) = 0.33$, $p = 0.724$, $\eta^2 = .008$; arm × sex: $F(1,81) = 0.18$, $p = 0.670$, $\eta^2 = .002$; age group × sex: $F(2,81) = 0.89$, $p = 0.413$, $\eta^2 = .022$; arm × age group × sex: $F(2,81) = 0.89$, $p = 0.415$, $\eta^2 = .021$) (see Figure 14 A).

Constant errors

The analyses showed no significant main effect of age group ($F(2,81) = 2.86$, $p = 0.063$, $\eta^2 = .066$), sex ($F(1,81) = 1.61$, $p = 0.208$, $\eta^2 = .019$) or arm ($F(1,81) = 0.93$, $p = 0.337$, $\eta^2 = .011$). Factors did not interact significantly with each other (arm × age group: $F(2,81) = 0.65$, $p = 0.524$, $\eta^2 = .016$; arm × sex: $F(1,81) = 0.04$, $p = 0.853$, $\eta^2 = .000$; age group × sex: $F(2,81) = 0.87$, $p = 0.423$, $\eta^2 = .021$; arm × sex × age group: $F(2,81) = 0.02$, $p = 0.985$, $\eta^2 = .000$) (see Figure 14 B).

Difference limen

There was no significant main effect of age group ($F(2,81) = .18$, $p = 0.831$, $\eta^2 = .004$), sex ($F(1,81) = .47$, $p = 0.495$, $\eta^2 = .006$) or arm ($F(1,81) = 3.22$, $p = 0.077$, $\eta^2 = .038$), as well as no interaction effect (arm × age group: $F(2,81) = 0.575$, $p = 0.565$, $\eta^2 = .014$; arm × sex: $F(1,81) = 0.11$, $p = 0.741$, $\eta^2 = .001$; age group × sex: $F(2,81) = 0.09$, $p = 0.909$, $\eta^2 = .002$; arm × sex × age group: $F(2,81) = 0.18$, $p = 0.837$, $\eta^2 = .004$) (see Figure 14 C).

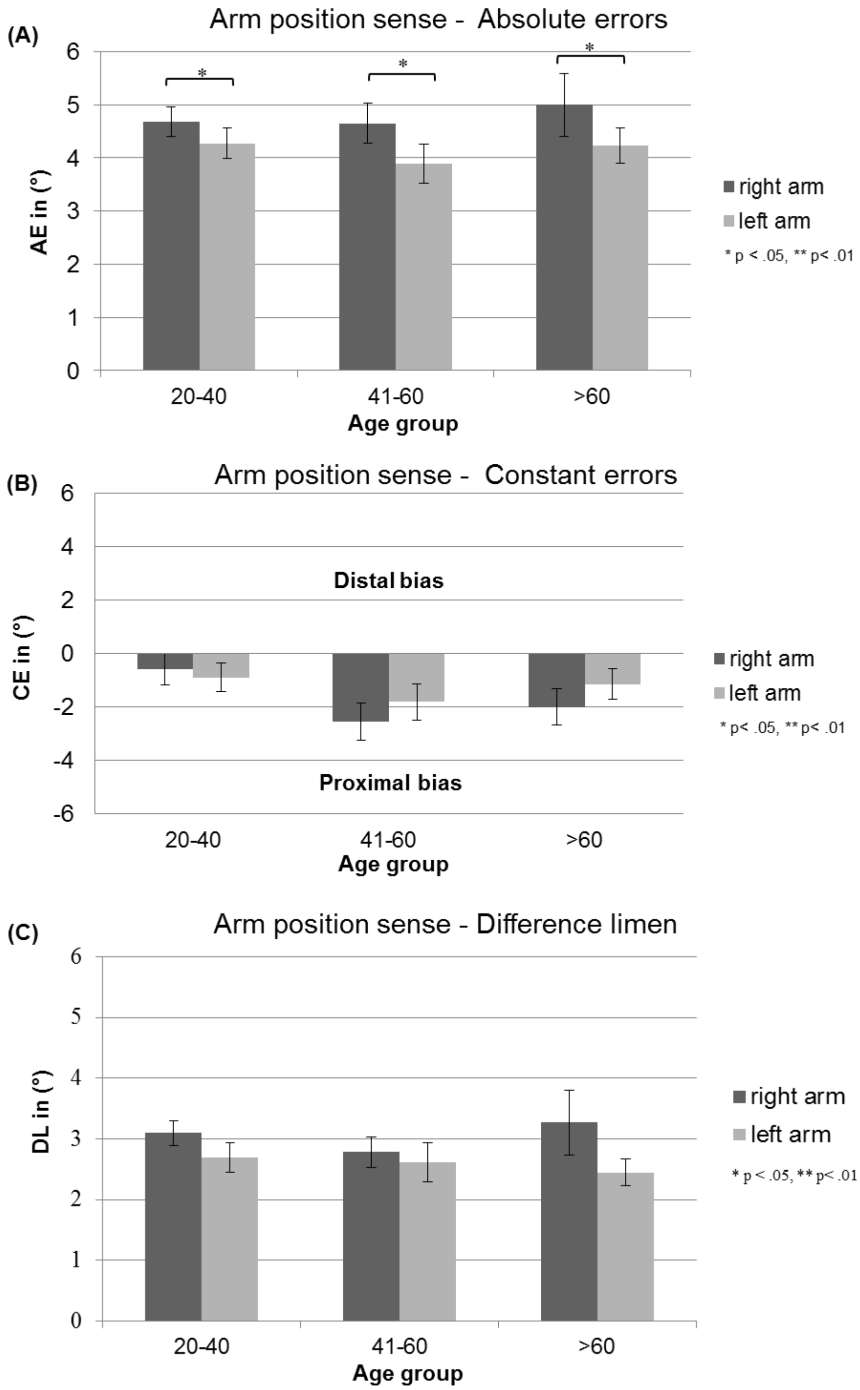


Figure 14 (A) *Mean absolute errors (AE; in degrees),* ***(B)*** *mean constant errors (CE; in degrees) and* ***(C)*** *mean difference threshold (difference limen, DL, in degrees) with standard error of the mean (SEM) of the three age groups of right and left arm. Negative errors indicate proximal deviations (towards the own body), positive errors distal deviations (away from the own body).*

Additional analyses

There were significant correlations (Spearman correlation coefficients) between the left and right arm, respectively AE (r_s = 0.29; p = 0.006), CE (r_s = 0.27, p = 0.01), and DL (r_s = 0.21, p = 0.049). There were no significant correlations between grip strength and CE of the right arm (r_s = 0.084, p = 0.453) or the left arm (r_s = -0.019, p = 0.867), suggesting that APS is independent of grip force.

One sample t-tests against zero revealed that the CE in the age group of 41-60 years differed significantly from zero for the right (T(21) = -3.61, p = 0.002, d = -2.55) and for the left arm (T(21) = -2.69, p = 0.014, d = -1.80). In the age group >60 years there was a significant difference from zero for the CE in the right arm (T(24) = -2.95, p = 0.007, d = -2.00) but not in the left arm (T(24) = -2.05, p = 0.051, d = -1-14). Hence deviations were into the *proximal* direction towards the own body in both arms for these two age groups. CE in the age group 21-40 did not differ significantly from zero neither for the right arm (T(39) = -0.97, p = 0.337, d = -0.57) nor for the left arm (T(39) = -1.69, p = 0.099, d = -0.90).

5.5 Discussion

The following results were found: (i) Healthy subjects show deviations in APS in both arms, especially in AE. (ii) There is no decrease in APS accuracy or precision with age. (iii) No significant sex differences in APS performance were found. (iv) AE were significantly higher in the dominant, right forearm as compared to the non-dominant, left arm in the right-handed participants. We will discuss these aspects consecutively below.

Arm position sense in healthy subjects

Normative data

The present study reports normative data of APS in the horizontal domain from a rather large group of healthy subjects up to an age of 77 years, assessed with a new device (APD), allowing to determine angular deviations with a resolution of 0.1°. We found slight deviations in APS from the visual reference in all three age groups of healthy subjects. These results are compatible with the findings reported by Fuentes and Bastian (2010) who also observed different variations in proprioception across space and task demands in healthy subjects. Such variant estimates of arm position – which often were towards the own body (hence proximal bias) - may represent a "safety mechanism" of the proprioceptive system to prevent injury to the limbs by shifting them towards the own body (Fuentes & Bastian, 2010).

The normative data obtained in our study could assist in providing information about the normal range in APS of healthy subjects of different ages. Moreover, they are suitable to track changes in the accuracy and precision of APS into the normal range of healthy subjects in patients due to therapeutic interventions, as e.g. recently demonstrated during and after GVS in patients with left spatial neglect following stroke (Schmidt et al., 2013a).

Apart from these clinical and practical aspects, our study contributes the surprising - at first glance - finding that healthy, dominant right-handers produced less absolute errors in the horizontal APS of their non-dominant, left arm in the absence of vision than of their preferred right arm, although they did not show differences in accuracy. This capacity was obviously unrelated to hand preference and grip force values, which were uniformly higher in the right arm in our right-handed sample. This finding corroborates a very similar finding from a recent study showing that healthy right-handers are not better in horizontal APS in their dominant, right hand as compared to their non-dominant, left hand (Schmidt et al., 2013a; Schmidt et al., 2013b). Recent studies revealed also that it depends on task demands which limb shows better performance in proprioceptive tasks (Goble & Brown, 2007; Goble & Brown, 2009; Goble, Lewis, & Brown, 2006). Interestingly, it is not always the dominant limb but rather the non-dominant, left limb in right-handers, especially in static, position-related proprioceptive sense (Goble & Brown, 2008), suggesting a dominance of preferred right arm/left hemisphere for motor action and a non-preferred left arm/right hemisphere sensory dominance for using proprioceptive feedback, especially in the absence of vision (Goble & Brown, 2008). The higher precision of APS in the left arm of healthy right-handers in the present study most likely reflects a superior hemispheric capacity of the healthy right hemisphere in this proprioceptive-spatial task. This result indicates a clear right hemisphere superiority for left APS in right-handers – at least for static endpoint position sense in the horizontal plane - and neatly fits to the more frequent and more severe deficits in APS for the left arm in stroke patients with left spatial neglect due to right hemisphere brain lesions (Schmidt et al., 2013a; Vallar et al., 1993a; Vallar et al., 1995).

Right- vs. left-handers

This asymmetry appears to be selective for right-handers, but not for left-handers (Schmidt et al., 2013b) and does not confirm the inverse asymmetry found for left-handers in proprioceptive target matching tasks (Goble, Noble, & Brown, 2009). In this recent study, right-handers showed a significant direction-specific bias in both forearms in APS, whereas left-handers did not have a significant deviation in any arm. Furthermore, GVS temporarily disrupted this proprioceptive ability of the left arm in dextrals but had no effect in the matched sinistrals. These findings point, first, to superior arm proprioception in left-handers for both arms and, second, to a greater susceptibility of the systems involved in the building-up and updating of cortical body representations by incoming sensory (vestibular) information in right-handers. This, in turn, is compatible with a right hemisphere dominance for vestibular functions in right-handers, because this unilateral, predominantly right hemisphere, vestibular cortical representation is easier to disturb by vestibular stimulation, and a differential, probably more bilateral vestibular organization in left-handers, that more easily compensates for such disturbing effects of vestibular stimulation on APS (Schmidt et al., 2013a). Recent studies neatly fit to this general picture showing that left-handers perform better in body-related cognition tasks, both on the behavioral (e.g. Hach & Schütz-Bosbach, 2010; Laeng & Peters, 1995; Linkenauger et al., 2009a) as well as on the neuroanatomical level (e.g. Amunts et al., 1996; Vingerhoets et al., 2012).

Proximal vs. distal biases

In order to analyze APS more precisely and to detect small deviations in APS in healthy subjects, we computed different types of errors (see Table 5). Concerning non-directional AE our healthy individuals showed deviations in APS which were, surprisingly, independent of age: right arm: 4.65°-4.99°, left arm: 3.89°-4.28°. Regarding signed errors, the finding that the mid-aged group showed significant deviations for both arms and the oldest age group in the right arm, hence in both cases towards the own body (proximal errors), suggest that these two age groups relied more on their own body as a reference frame for position sense as compared to the youngest age group. This could be interpreted as a slight age effect. However, a closer look at the data (see Figure 14 B) shows that all age groups manifested a proximal bias in APS towards their body for both arms: right arm: -2.55°- (-.57°), left arm: -.89°- (-1.81°). This finding corresponds neatly with findings of recent studies concerning APS in healthy right-handers (Schmidt et al., 2013b) as well as in stroke patients with left neglect (Schmidt et al., 2013a; Vallar et al., 1993a). Apparently, the own body plays an important role for determining the position of own limbs in the absence of vision in the personal near space. This proximal error in APS might be interpreted as a kind of “productive” abnormality which is due to the importance of our own body as a reference for updating the position of body segments in relation to it.

Age

The most common assessment of proprioception in the elderly is assessment of the static position of limb segments (Goble et al., 2009a). Interestingly, we did not find a significant decrease in APS accuracy and precision with age. This finding is at first glance at variance with almost all other studies conducted on this topic, which show a clear age effect on proprioceptive abilities (Adamo et al., 2007), and a significant deterioration of limb position sense with age (Adamo et al., 2007; Meeuwsen, Sawicki, & Stelmach, 1993; Stelmach & Sirigu, 1986; for a review, see Goble et al., 2009a). Interestingly, this deterioration in the ability to sense the position of a body segment with age is typically found in studies which used limb matching tasks (using both arms), as mentioned in the introduction, but not in studies using proprioceptive matching tasks with visual reference points where subjects indicate the felt position of their limb relative to a visual marker (Cressman, Salomonczyk, & Henriques, 2010). Moreover, the extent to which limb position sense is influenced by aging depends on aspects like the tested joint/limb segment, active/passive task, kind of analyzed error (for a review, see Goble et al., 2009a) or task goal (Jones et al., 2012). Moreover, reduced proprioceptive acuity may also reflect age-related changes in cognitive functions (i.e. decisional factors, working memory) due to demands of the assessment methods as mentioned above. To circumvent such potentially influential factors, the examination of APS with the APD was kept as short and simple as possible. Therefore, potential confounding factors such as decreased memory abilities or reduced sustained attention with age (Reuter-Lorenz & Sylvester, 2005), or age-related deteriorations in cognitive processing which influence sensorimotor functions (Li & Lindenberger, 2002) were minimized in our sample, in contrast to ipsilateral remembered matching tasks. The fact that assessing APS with the APD requires matching of each forearm´s position in relation to a visual reference point in peripersonal space and not in relation to the other arm, avoids another confounding factor of contralateral concurrent matching tasks, namely the interhemispheric transfer of proprioceptive feedback due to the age-related degeneration of the corpus callosum (Ota et al., 2006; Salat et al., 2005). Adamo and colleagues (2007) examined age effects on position sense for the elbow under three matching conditions which varied in requirements of memory and interhemispheric transfer: ipsilateral remembered, contralateral concurrent and contralateral remembered condition. They found a main effect of age on absolute matching errors with greatest errors in the most demanding condition, which required both memory and interhemispheric transfer, in the older age group, suggesting that these tasks require more than merely position sense. Moreover, recent studies did not find age effects in all kinds of analyzed errors of position sense of specific limbs, e.g. of the finger (Ferrell, Crighton, & Sturrock, 1992) or the foot (Meeuwsen et al., 1993), when constant, direction-specific errors were analyzed, in contrast to unsigned errors. Therefore, the missing age effect in the present study can be explained by interaction effects of computed outcome parameter and the analyzed limb. This is consistent with the result that younger and older aging people show similar proprioceptive acuity when APS is assessed in a visual-to-proprioceptive matching task, such as in the APD in the present study (Cressman et al., 2010; Ferrell et al., 1992), without requiring proprioceptive memory or interhemispheric transfer. This finding suggests that the extent of proprioceptive recalibration with visual reference markers is independent of age and remains largely constant throughout the lifespan. Another explanation for the lack of age effects in the present study as compared to previous studies could be the different task demands as proposed by Cressman and colleagues (2010). According to Fuentes and Bastian (2010), endpoint limb positions are more robust against deteriorations due to age than angle position information. They argue that due to the greater behavioral need to estimate limb positions than joint angles, the brain may immediately encode limb position from peripheral sensory signals as compared to joint angle estimates which have to be extracted from these representations.

Apart from task-specific effects, there is clear evidence for age-related changes in the neural basis of proprioceptive processes (e.g. Goble et al., 2012), namely degenerative and plastic-adaptive processes in the aging proprioceptive system, both in the central as well as in the peripheral nervous system and muscular system (Adamo et al., 2007; for a review, see Goble et al., 2009a). This raises the question why some studies did not find age effects in proprioceptive matching tasks. One potential explanation may be that older subjects can compensate for this decline, due to implicit learning mechanism throughout life. This question will be a major challenge for future studies and could also inform us how proprioceptive impairments can be prevented or treated by exploiting such compensatory mechanisms.

Sex

No sex-specific differences were found in APS performance in the present study. This negative finding contradicts the widely shared assumption that males have better spatial skills as compared to females (Voyer, Voyer, & Bryden, 1995). However, previously performed studies have not yet been able to explain the sex-specific differences in these tasks and simply assumed sex as a causal factor. Contreras, Martinez-Molina and Santacreu (2012) have studied this issue using three different spatial matching tasks. They found that sex was not important for correctly solving these tasks, but rather a specific type of process that determined participants´ efficiency in solving a spatial task.

Therefore, the magnitude of the advantage that males may have over females crucially also depends on the type of spatial task. Accordingly, limb position sense imposes demands on the proprioceptive system in the personal space and might require the same underlying cognitive abilities in males and females and activate the same type of processes for solving the task in both sexes. This may explain the lack of any sex effects in our APS task.

Clinical issues

Impaired limb position sense is a frequent and debilitating sequel after stroke (Carey, 1995; Shah, 1978; Smith et al., 1983). Positions sense disorders are likely to be caused by a failure to link somatosensory with egocentric information (Vallar et al., 1993a). Patients show constraints in performing activities of daily living, have problems in safety, postural stability and motor functions (Carey, 1995; Carey et al., 1996; Dijkerman & De Haan, 2007). In the clinic, patients with impaired APS show poorer and longer motor recovery of the hemiparetic or hemiplegic arm (De Weerdt et al., 1987; Feys et al., 2000; Kuffosky et al., 1982; Wade et al., 1983; Wadell et al., 1987).

Previous studies found that left-sided visuospatial neglect after right brain damage is functionally associated with impaired arm position judgments in the contralesional arm (Schmidt et al., 2013a) and also with problems in other body-related spatial tasks such as left tactile extinction (Schmidt et al., 2013d) or in identifying left human hands (Reinhart et al., 2012). This proprioceptive deficit can be temporarily restored by GVS (Schmidt et al., 2013a). This improvement may be either due to a more veridical perception of their contralesional arm, or of the target LED, or of both components.

Relation to other body cognition disorders

The right hemisphere superiority for proprioception in healthy right-handers - found in this but not in all other studies - and the greater left-sided impairments after right hemisphere lesions are compatible with other “dysfunctions” of the right cerebral hemisphere that result in left-sided body-related disorders such as somatoparaphrenia (Gandola et al., 2012) or neuropsychiatric disorders without a history of brain damage such as xenomelia (Berti, 2013; Hilti et al., 2013). Xenomelic subjects, who desire the amputation of healthy limbs, show a reduced activation in the right superior parietal cortex during tactile stimulation of the affected leg (McGeoch et al., 2011). Hilti and colleagues (2013) studied the brain areas associated with xenomelia for the left arm in 13 patients and found predominantly right hemisphere brain abnormalities resulting in the strong desire for amputation of left-sided limbs. These brain areas correspond neatly with those identified in patients with somatoparaphrenia, where the patient feels that a paralyzed limb does not belong to his body (Gandola et al., 2012; Hilti et al., 2013) and has a blurred distinction between corporeal and extracorporeal objects, that is often associated with left motor and somatosensory deficits and neglect (Ronchi & Vallar, 2010). In turn, this lesion pattern, involving a fronto-temporo-parietal network in the right cerebral hemisphere, is typically associated with spatial neglect, hemiplegia and anosognosia (Gandola et al., 2012), which confirms the importance of right hemisphere for productive behaviors in personal and near extrapersonal space.

The overestimation of body size in patients with anorexia nervosa is proposed to be, besides psycho-affective causes, the result of impaired neural mechanisms supporting body representation, comparable to patients following stroke. In an interesting, innovative study Nico and colleagues (2010) compared body knowledge in anorexics, healthy subjects and patients with lesions of either the left or right parietal lobe after stroke. They found that patients with anorexia nervosa and those with right parietal damage selectively underestimated the extent of their left body boundary in a similar way. This finding confirms the important role of the right parietal cortex in building-up and updating of the representation of the body and peripersonal space (Graziano & Gross, 1995), also in anorexics (Grunwald et al., 2002).

Limitations

We have tested the APS using a visual reference (LED) while most of the other studies on arm proprioception use nonvisual tasks. This may have led to different results.

As another limitation, we did not collect data of the vertical or sagittal dimension and, therefore, we are not able to make conclusions about the generalization of our results on the entire egocentric coordinate system, as suggested in other studies (e.g. Vallar et al., 1995).

Moreover, we cannot exclude the possibility that we may have missed age-related deteriorations in proprioception in the form of an increased variability as a result of the limited number of trials in our assessment with the APD, as found with other devices and more trials in elderly subjects (Cressman et al., 2010).

5.6 Conclusion

In summary, this study provides normative data from healthy subjects for APS of a wide age range (20-77 years) for both arms in the horizontal plane. APS in our healthy subjects was not significantly influenced by age or sex, but all right-handed healthy subjects showed significantly more accurate performance in their non-dominant (left) arm. This indicates a clear right hemisphere superiority for left APS in right-handers. This finding neatly fits to the more frequent and more severe left-sided, body-related deficits in personal/peripersonal space tasks observed in patients suffering from right hemisphere stroke (e.g. anosognosia for left hemiparesis, somatoparaphrenia, body neglect) as well as to the right hemisphere abnormalities reported in some neuropsychiatric conditions associated with body perception or body representation deficits (e.g. anorexics).

6 Study 4: Now you feel both: galvanic vestibular stimulation induces lasting improvements in the rehabilitation of chronic tactile extinction

Schmidt, L., Utz, K. S., Depper, L., Adams, M., Schaadt, A.-K., Reinhart, S., & Kerkhoff, G. (2013). *Frontiers in Human Neuroscience, 7:90*. doi: 10.3389/fnhum.2013.00090

6.1 Abstract

Tactile extinction is frequent, debilitating and often persistent after brain damage. Currently, there is no treatment available for this disorder. In two previous case studies we showed an influence of GVS on tactile extinction. Here, we evaluated in further patients the immediate and lasting effects of GVS on tactile extinction. GVS is known to induce polarity-specific changes in cerebral excitability in the vestibular cortices and adjacent cortical areas. Tactile extinction was examined with the Quality Extinction Test (QET) where subjects have to discriminate six different tactile fabrics in bilateral, double simultaneous stimulations on their dorsum of hands with identical or different tactile fabrics. Twelve patients with stable left-sided tactile extinction after unilateral right hemisphere lesions were divided into two groups. The GVS group (N=6) performed the QET under six different experimental conditions (two Baselines, Sham-GVS, L-GVS, R-GVS, and a follow-up test). The second group of patients with left-sided extinction (N=6) performed the QET six times repetitively, but without receiving GVS (control group). Both R-GVS as well as L-GVS (mean: 0.7 mA) improved tactile identification of identical and different stimuli in the experimental group. These results show a generic effect of GVS on tactile extinction, but not in a polarity-specific way. These observed effects persisted at Follow-up. Sham-GVS had no significant effect on extinction. In the control group, no significant improvements were seen in the QET after the six measurements of the QET, thus ruling out test repetition effects. In conclusion, GVS improved bodily awareness permanently for the contralesional body side in patients with tactile extinction and thus offers a novel treatment option for these patients.

6.2 Introduction

In daily life touch is important in many situations, i.e. when we grasp objects, manipulate them, or identify them, e.g. when retrieving a key from our pocket. Brain lesions, due to stroke, head trauma or other causes impair a variety of somatosensory abilities dramatically in more than 50% of patients (Van Stralen, van Zandvoort, & Dijkerman, 2011). Among these impairments, tactile or somatosensory extinction is a frequent disorder (Kerkhoff et al., 2011a). Extinction of sensory stimuli - in whatever modality - is defined as the inability to process or attend to the more contralesionally located stimulus when two stimuli are simultaneously presented. By definition, the processing of a single stimulus should only be marginally impaired, thereby ruling out gross elementary sensory deficits (i.e. hemianopia, hemianaesthesia, unilateral hearing loss). Extinction may occur in the visual (Conci et al., 2009), auditory (Deouell & Soroker, 2000), olfactory (Eskenazi, Cain, Novelly, & Friend, 1983) or tactile modality (Berti et al., 1999; Maravita et al., 2003). Tactile extinction is frequently found after unilateral, mostly right-sided brain lesions (70%, Schwartz et al., 1977; Schwartz et al., 1979; Heldmann et al., 2000), is a negative predictor for the patient´s outcome (Rose et al., 1994) and often persists for years after lesion (Heldmann et al., 2000). Causative lesions are found in the frontal, parietal or temporal cortex (Deouell & Soroker, 2000; Schwartz et al., 1977) and the basal ganglia (Vallar, Rusconi, Bignamini, & Geminiani, 1994). In addition, anterior callosal lesions may disrupt the processing of the left-hand tactile stimulus (Schwartz et al., 1979), which may explain the more frequent occurrence of tactile extinction on the left body side than on the right (Schwartz et al., 1979). Moreover, tactile extinction does not only occur when the patient has to *detect* tactile stimulation (Bender, 1952), but also appears when he/she has to *discriminate* different tactile surfaces (Schwartz et al., 1977), and even occurs when a patient simultaneously explores two common household objects actively by touch (Berti et al., 1999). Tactile extinction is modulated by stimulus properties (i.e. additional sensory stimulation of the hand) *and* response factors (verbal vs. nonverbal output; cf. Vaishnavi, Calhoun, Southwood, & Chatterjee, 2000). The latter indicates that interference between both stimuli can even occur at a post-perceptual level, probably close to the language system.

Two main explanations of extinction have been proposed: sensory (Bender, 1952) and attentional theories (Vallar et al., 1994). While the prior explains extinction as the result of a weakened sensory integration process, the latter holds that elementary sensory abilities may be completely intact, and yet extinction occurs. In favor of the latter account, several studies have shown that early sensory or pre-attentive processes are often reasonably intact in patients with visual extinction (Conci et al., 2009). Various stimulation manoeuvres such as CVS (Vallar et al., 1993b), optokinetic stimulation (Nico, 1999), repetitive peripheral magnetic stimulation (Heldmann et al., 2000), visuomotor prism adaptation (Maravita et al., 2003) or positioning of the “extinguishing” limb in the ipsilesional hemispace (Aglioti, Smania, & Peru, 1999; Sambo et al., 2012) significantly modulate tactile extinction. This accords with proposals that somatosensory deficits in right hemisphere patients may relate, at least partially, to neglect (Vallar, 1997), which can be significantly modulated by sensory stimulation manoeuvres (Kerkhoff, 2003). Yet, few studies have so far evaluated to which degree tactile extinction can be *permanently* cured with such methods. A remarkable case study (Dijkerman et al., 2004) reported a long-lasting (for at least one to three weeks), beneficial effect of only *two* sessions of prism adaptation on somatosensory functions (pressure sensitivity and proprioception), indicating a considerable capability for the treatment of these disorders. Other sensory stimulation techniques might induce similar beneficial effects on somatosensory deficits after stroke, thus offering a potential treatment choice beyond the classic therapies already available for a longer time (cf. Carey, 1995; Carey & Matyas, 2005).

One such technique is GVS. GVS is a non-invasive vestibular stimulation that is, unlike *CVS*, easier to use, lacking adverse side effects (with currents < 1.5mA) and therefore appears more appropriate for *repetitive* treatment without habituation effects (Utz et al., 2010; Utz et al., 2011b). Practically, weak direct currents are delivered via two electrodes of different polarity (anode and cathode) attached to the two mastoids behind the ears. On the neural level, GVS induces polarisation effects in the vestibular nerves, leading to an activation of the semicircular canals, otolith organs and the adjacent vestibular nerves (Fitzpatrick & Day, 2004). Cortical activation is seen in the posterior insula and the temporo-parietal region in healthy subjects during GVS. Further activation was found in the middle and superior temporal gyrus, the putamen, the anterior cingulate gyrus and thalamus (Lobel et al., 1998; Bense, Stephan, Yousry, Brandt, & Dieterich, 2001). Interestingly, *bilateral* activations of vestibular cortices are obtained by applying left-cathodal/right-anodal GVS (L-GVS), whereas *unilateral*, right-hemispheric activations are induced by right-cathodal/left-anodal GVS (R-GVS) (Dieterich et al., 2003; Fink et al., 2003).

Only a few studies have so far evaluated the potency of GVS in patients with neglect, extinction and related spatial disorders. Rorsman, Magnusson and Johansson (1999) showed a transient reduction of visual neglect symptoms in patients with neglect (i.e. line cancellation) during R-GVS. A recent case study found a significant improvement in visuo-constructive deficits (copy of Rey-figure) during GVS (Wilkinson, Zubko, Degutis, Milberg, & Potter, 2010). Recently, we have already been successful in modulating neglect with GVS: one 20 minutes session of R-GVS temporarily reduced the ipsilesional bias in line bisection (Utz et al., 2011a), whereas 20 minutes of L-GVS normalized the profound deficits in left arm position sense in patients with left neglect (Schmidt et al., 2013a).

As outlined above, GVS can modulate the thalamocortical network of the brain in a polarity-specific way, either by activation (anodal stimulation) or de-activation (cathodal stimulation) (Utz et al., 2010). As tactile extinction is viewed by some theories (Schwartz et al., 1979) as resulting from an imbalance of somatosensory inputs received simultaneously from both hands we hypothesized that GVS may re-balance this disturbed weighting via activations of certain brain areas involved in tactile extinction or inhibition of mirror-symmetric areas in the intact hemisphere. In two recent case studies we could show a lasting influence of a few sessions of GVS on tactile extinction (Kerkhoff et al., 2011a), thus serving as an initial proof-of-principle test of the therapeutic efficacy of GVS.

Furthermore, promising effects of GVS in the modulation and/or treatment of other symptoms associated with neglect syndrome (Kerkhoff & Schenk, 2012) initiated to study the effects of GVS on tactile extinction in a larger sample, including a nontreated control group showing the same disorder as the treated, experimental group. From available literature on GVS we expected a *transient* reduction of left-sided (left-hand) extinction errors under GVS, but no specific effect on right-sided (right-hand) errors induced by GVS. Regarding polarity we had no directional hypothesis as some of the few available studies on GVS showed improvements during L-GVS, whereas others showed improvements during R-GVS (as mentioned above). In the present study we therefore explored the effects of GVS on tactile extinction in two comparable samples of patients with right-sided stroke (experimental group: N=6, control group: N=6), all showing left-sided tactile extinction. Apart from *online*-stimulation effects (*during* GVS) we were particularly interested in the *after*-effects of GVS and potential enduring treatment effects on tactile extinction in the experimental group. In the control group, the influence of retesting was analyzed by testing the patients six times in an identical study protocol, but without GVS (see below, Figure 15).

6.3 Materials and methods

Participants

A total of 12 patients with right hemisphere stroke and left-sided tactile extinction as determined in the QET (see below) were included in the study. Six patients served as the experimental group (four males, GVS group) and received different protocols of GVS, while the other six patients served as the control group (three males, control group) which was retested six times with the QET in identical schedule to rule out test repetition and other unspecific effects (Table 6). Allocation of patients into the two patient groups was done in the following way: first, six experimental patients with extinction were treated with GVS as described below; second, six control patients with extinction were recruited in order to match the sample of experimental patients in demographic and clinical variables and extinction severity. Time intervals between the six different sessions were identical between the two patient groups. They did not differ with respect to age ($T(10) = 1.526$, $p = .236$), sex (χ^2 $(df=1) = 3.43$, $p = .558$) or time since lesion ($T(10) = 1.541$, $p = .154$). They did not differ in their Baseline performances in the QET, neither for their left or right hand nor for different or identical materials (all $p_s > .05$). All subjects except one were right-handed according to the Edinburgh handedness questionnaire (Salmaso & Longoni, 1985) and had no history of psychiatric disorders or dementia. A visual neglect screening including digit cancellation (cancel all digits “5” out of 200 single digits on a 21 x 29.7 cm large white paper, ten targets per hemispace), horizontal line bisection of a 20 cm x 0.5 cm long black line and text reading of a 180 word reading text were conducted in all patients (details for these tests see Schmidt et al., 2013a). All investigations were performed in accordance with the Declaration of Helsinki II and all participants gave their informed written consent before examination. A positive, written ethical approval by the local medical ethical committee (Ärztekammer Saarland) was available for the use of subliminal GVS in brain-damaged patients. No patient was enrolled in any other neuropsychological treatment (attention, neglect) or motor therapy (physiotherapy, occupational therapy) during the course of the study.

Table 6 *Clinical and demographic data of 12 patients with left-sided tactile extinction due to a right hemisphere brain lesion. Abbreviations: ICB: intracerebral bleeding; PCI: posterior cerebral artery infarction; MCI: middle cerebral artery infarction. Visual neglect: diagnosis based on conventional tests of digit cancellation, line bisection and reading (for details see Schmidt et al., 2013a); Tactile extinction: as tested by tactile stimulation of the patient´s dorsum of hands by light touch.*

Patient	Group	Age, Sex	Handed-ness	Aetiology	Lesion, Lesion Age (months)	Motor Deficits	Visual Field	Digit cancellation omissions L/R max. (10/10)	Line bisection (20 cm, deviation in mm)	Neglect dyslexia	Visual Neglect	Tactile extinction
1-LA	GVS	70, male	Right-hander	ICB	Right fronto-parietal, 60.3	Left hemiparesis	Normal	0/0	-3	No	Yes	Yes
2-RE	GVS	45, female	Right-hander	ICB	Right frontal, right temporal, 71.2	Left hemiparesis	Left hemianopia, 10°	1/1	+2	No	Yes	Yes
3-KA	GVS	66, male	Right-hander	ICB	Right parietal, 6	Left hemiparesis	Normal	4/1	+13	Yes	Yes	Yes
4-NI	GVS	51, female	Right-hander	MCI	Right fronto-parietal, 6	Left hemiparesis	Normal	5/2	-10	No	Yes	Yes
5- SC	GVS	72, male	Right-hander	PCI	Right occipital, right thalamus, 25	Normal	Left hemianopia	4/1	-12	Yes	Yes	Yes
6-Kla	GVS	47, male	Left-hander	Thala-mus infarc-tion	Right pulvinar, 2.3	Normal	Left upper quadranopia	2/1	-7	Yes	No	Yes
Mean	**N = 6**	**58.3 (SD=12.4)**			**28.5 (SD=30.2)**			**3/1**	**-2.8**			
7-ME	Control	59, male	Right-hander	ICB	Right fronto-parietal, 8	Left hemiparesis	Normal	2/2	-4	Yes	No	Yes
8-TA	Control	47, female	Right-hander	ICB	Right basal ganglia, 12	Left hemiparesis	Normal	2/1	-2	No	Yes	Yes
9-CR	Control	68, male	Right-hander	PCI	Right thalamus and right occipital, 5	Normal	Left hemianopia	5/2	+11	Yes	Yes	Yes
10-WI	Control	45, male	Right-hander	MCI	Right parietal, 15	Left hemiparesis	Left lower quadranopia	4/2	+9	Yes	Yes	Yes
11-TU	Control	47, female	Right-hander	ICB	Right parietal , 5	Left hemiparesis	Left lower quadranopia	4/2	+10	Yes	Yes	Yes
12-HA	Control	25, female	Right-hander	ICB	Right basal ganglia, 11	Normal	Normal	1/1	+3	No	No	Yes
Mean	**N = 6**	**48.5 (SD=14.6)**			**9.3 (SD=4.0)**			**3/2**	**+4.5**			

Quality Extinction Test

The Quality Extinction Test (QET; Schwartz et al., 1977) is a sensitive tactile extinction test that requires the subject to identify and name six different tactile surfaces first in unilateral trials on the left and right dorsum of hands and then in double simultaneous stimulation trials (DSS) with the same materials. Previous studies with the QET have shown that patients with right frontal or right parietal lesions consistently show marked left-sided tactile extinction in those trials with *bilateral* different stimuli while showing normal performance in unilateral target presentations (Schwartz et al., 1977; Schwartz et al., 1979). Subsequent studies with the QET provided evidence that tactile extinction is modulated by somatosensory input delivered via repetitive peripheral magnetic stimulation of the left forearm (Heldmann et al., 2000; Kerkhoff, Heldmann, Struppler, Havel, & Jahn, 2001). Moreover, we found that apart from those bilateral trials with *different* fabrics (e.g.: left hand: sandpaper, right hand: silk) those bilateral stimulations using *identical* fabrics (e.g.: both hands: silk) also made a useful diagnostic contribution, although they appeared to be easier to solve (cf. Kerkhoff et al., 2011a).

The present version of the QET includes six different materials varying in tactile quality (soft sandpaper, silk, fleece, plastic, jute and rubber gum) that were attached singly to wooden boards (size: 15 x 10 cm). Patients placed their hands with palms down and beside each other (hence in the normal “anatomical” position) on the table in front of the experimenter. During all testing sessions patients were blindfolded and wore a closed head-phone in order to prevent visual and auditory cues during the tactile stimulation procedure. Patients were instructed to identify and name the six different tactile materials used throughout the test. To this purpose, single boards were moved slowly by the experimenter with a speed of 2 cm/sec from proximal to distal across the dorsum of either the left or right hand. Each material was presented three times in this way and the patients had to report the material verbally. Twelve unilateral trials were run for each hand separately per patient, for every testing session. After these unilateral trials, which served to assess unilateral tactile performance, bilateral stimulation trials were performed. Here, two boards were presented simultaneously, one to each hand, and the patient had to name the material(s) he/she recognized on each hand. A total of 36 bilateral trials were performed in each complete test: 18 trials with different and 18 trials with identical materials delivered to both hands. Unilateral trials were not repeated during the experimental sessions as normal or near-to-normal unilateral performance had been established already in the two Baseline sessions before GVS. Moreover, the unilateral trials were of no particular interest in this study after normal unilateral performance had been established in all patients. Patients were unaware of the fact that one half of the trials were performed with identical and the other half with different tactile materials as both were intermingled within every session, but they were instructed that materials can be identical or different for both hands. If patients could not identify correctly one or both of the materials in a trial with bilateral stimulation, an extinction response was scored for the corresponding side. Thereafter, the next bilateral stimulation trial was performed. No attempt was made to force the patients to guess in case they were unable to verbally identify the material. The patients were not forced to guess whether the two stimuli were same or different in case of missing verbal response for one side. No time constraints were imposed and no feedback was given during testing. The percentage and raw score of left- and right-sided extinction during DSS with *different* tactile stimuli (based on 18 trials) as well as during DSS with *identical* tactile stimuli (based on the other 18 trials) were computed for every session. Note that the QET – in contrast to conventional tactile extinction procedures using light touches of the patient´s hands – requires *discrimination* of six different tactile materials and finally their verbal identification. Therefore, a higher degree of error rates may be found, including some ipsilesional errors as well (Heldmann et al., 2000). Chance level, i.e. when the patient is guessing, is 16.6% in this task.

Galvanic vestibular stimulation (GVS)

Bipolar galvanic vestibular stimulation was delivered by a constant direct current (DC) stimulator (9-voltage battery, Type: ED 2011, producer: DKI GmbH, DE-01277 Dresden, Germany). The tap water-soaked sponge-covered electrodes (60 mm × 40 mm) were fastened on the skin over each mastoid (binaural stimulation) in order to activate the vestibular system. For L-GVS the cathode was placed on the left mastoid and the anode on the right, whereas for R-GVS this electrode setup was reversed. In the Sham-GVS condition, the two electrodes were positioned as in the L-GVS condition, except that no electric current was applied in order to rule out potential placebo-stimulation effects. We stimulated below the sensation threshold (subliminal) so that the subject was not aware of any electrical stimulation in any experimental or Sham condition (Utz et al., 2010). As there is evidence that even subtle attentional cues can modulate neglect and extinction (Riddoch & Humphreys, 1983), we employed this subliminal stimulation as it elegantly circumvents potential attentional cueing effects that might occur with *suprathreshold* stimulation. A switch on the stimulation device delivered current at an individually adjusted level to the patients. The individual threshold was determined by slowly increasing current intensity in steps of 0.1 mA until the patient indicated a tingling. Current was then reduced until the patient indicated that the sensation had disappeared. This procedure was repeated a second time and the mean of both threshold values was defined as the individual threshold. Individual thresholds of each patient were determined at the beginning of both stimulation sessions (L-GVS, R-GVS) in order to exclude suprathreshold stimulation caused by reduced thresholds for GVS (see results, below). Finally, in all conditions, the GVS stimulator was never visible for the patients.

Experimental Design

Patients in both groups participated in six different sessions (see Figure 15 for an outline of the design). In the control group, six investigations were performed with the QET at six different time-points of measurement (TP, 1-6) without GVS stimulation. In contrast, patients in the experimental (GVS) group performed two Baseline sessions without GVS. In session three to five, they performed the QET again while receiving either L-GVS, R-GVS or Sham-GVS, respectively in a pseudo-randomized sequence to control for order effects. Subjects were blind to the type of stimulation received. A follow-up was conducted 84 days (= 2.8 months (mean); range: 35-147 days) after the fifth testing session in all subjects (hence after the last GVS session in the experimental group and after TP5 in the control group). A two-day interval (min. 48 hours) was established between sessions to avoid carry-over effects. Importantly, the timing of testing sessions was identical in both samples (see Figure 15).

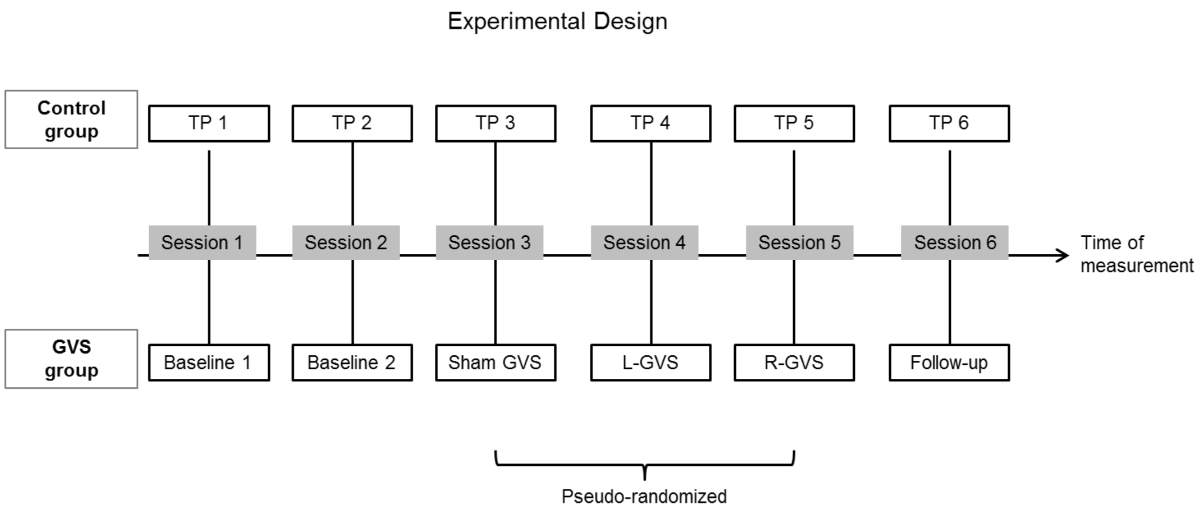


Figure 15 *A schematic overview of the experimental design: the galvanic vestibular stimulation (GVS) conditions performed with the six experimental patients with extinction and the different time-points of measurement (TP) performed with the six control patients with extinction, respectively in six different sessions. Abbreviations: L-GVS: left-cathodal/right-anodal GVS; R-GVS: right-cathodal/left-anodal GVS; Sham: Sham stimulation with GVS but without the application of current; Follow-up: Mean follow-up 2.8 months (84 days) after GVS.*

Statistics

All analyses were carried out using SPSS, version 19. First, we calculated extinction errors (in %) in the QET, separately for the 18 different and 18 identical bilateral trials, for each hand and each group. Repeated-measures analyses of variance (ANOVAs) with the between factor “group” (GVS group, control group) and the within factor “GVS condition/TP”

(Baseline1/TP1, Baseline2/TP2, Sham/TP3, L-GVS/TP4, R-GVS/TP5, Follow-up/TP6) were carried out separately for the right and left hand and for different and identical stimuli. Subsequent comparisons (ANOVAs and Bonferroni-adjusted t-tests for multiple comparisons (Holm, 1979)) were computed for a more specific examination of significant results. The alpha-level was set at $p = .05$, two-tailed for all analyses.

6.4 Results

Unilateral trials

In the 24 unilateral trials (12 unilateral trials per measurement × two measurements) each of the 12 patients scored > 95% correct for the left hand and > 98% for the right hand in the QET, thus showing normal or close-to-normal unilateral tactile identifications for both hands.

Analysis of Baseline 1 versus Baseline 2

ANOVAs with the between factor “group” (GVS group, control group) and the within factor “TP” (Baseline1, Baseline2), separately for different and identical materials and for each hand, revealed no significant effects of these factors, suggesting that there were no differences between the two first time points of assessment (Baseline1, 2) in the two groups (largest $F = 3.88$, smallest $p = .077$).

Individual threshold values and side effects of GVS

The mean current level at GVS threshold in the GVS group was 0.7 mA (range: 0.5-0.8 mA). This averaged threshold did not differ significantly between L-GVS (TP4) and R-GVS (TP5) condition ($Z = -1.0$, $p = .317$). A 34-items-questionnaire regarding possible side effects of GVS stimulation, which included items about fatigue, dizziness, vision and sleep disturbances, concentration difficulties, pain, skin disturbances, burning sensations etc. (cf. Utz et al., 2011b) was read by the examiner to all six patients after every real and Sham stimulation. No adverse effects were reported by any of the six experimental patients during or after GVS, except a slight tingling at the beginning of stimulation in the course of the individual threshold determination that was not negatively evaluated, but rather indicated that real current was delivered during GVS stimulation. Table 7 summarizes the individual and mean threshold values as well as side effects in the experimental group.

Table 7 *Individual and mean threshold values (milliAmpere, mA) for subliminal GVS conditions for patients in the GVS group and mean number of side effects (%) according to the 34-items-questionnaire, averaged over the GVS group and separately for each GVS condition. Abbreviations: L-GVS: left-cathodal/right-anodal GVS; R-GVS: right-cathodal/left-anodal GVS.*

Patient	L-GVS	R-GVS
Threshold values (mA)		
1-LA	0.5	0.6
2-RE	0.5	0.5
3-KA	0.8	0.8
4-NI	0.7	0.7
5-SC	0.8	0.8
6-KL	0.6	0.6
Mean	0.65	0.67
Side effects (%)	0	0

Bilateral different tactile stimulation

Right hand

The analysis of extinction errors during bilateral stimulation with *different* tactile stimuli of the right hand did not show statistically significant main effects of GVS condition/TP ($F(5,50) = 1.01$, $p = .424$, $\eta^2 = .091$) or group ($F(1,10) = 0.14$, $p = .718$, $\eta^2 = .014$) or a significant GVS condition/TP × group interaction ($F(5,50) = 1.03$, $p = .407$, $\eta^2 = .094$) (see Figure 16 A).

Left hand

In contrast, the analysis of left hand extinction scores during bilateral stimulation with *different* tactile materials yielded a significant main effect of GVS condition/TP ($F(5,50) = 5.99$, $p = .003$, $\eta^2 = .375$), of group ($F(1,10) = 8.76$, $p = .014$, $\eta^2 = .467$) as well as a significant interaction between these two factors ($F(5,50) = 4.17$, $p = .015$, $\eta^2 = .294$). Subsequent ANOVAs were carried out separately for the two patient groups with the factor GVS condition/TP to examine simple main effects. They yielded a significant main effect of GVS condition/TP only for the GVS group ($F(5,25) = 5.57$, $p = .001$, $\eta^2 = .527$) but not for the control group ($F(5,125) = 1.23$, $p = .326$, $\eta^2 = .197$). Subsequent t-tests analyzing the extinction errors differences between different GVS conditions/TP in the GVS group showed significant improvements in left-sided extinction in the L-GVS ($T(5) = 7.53$, $p = .001$), the R-GVS ($T(5) = 3.43$, $p = .019$) and the Follow-up ($T(5) = 3.12$, $p = .024$) condition as compared to Baseline1. Likewise, patients in the GVS group showed a less severe extinction in the L-

GVS as compared to the Sham condition (T(5) = 2.91, p = .034). The remaining comparisons did not show any significant differences between any of the conditions (largest T = 2.28, smallest p = .071) (see Figure 17 A). There were no differences between extinction errors in the L-GVS and R-GVS condition for the left hand in different materials (T (5) = -.63, p = .558). Table 8 (below) summarizes the results of the paired comparisons in the GVS group for the left hand, for easier orientation.

Bilateral identical tactile stimulation

Right hand

There were no significant effects of GVS condition/TP (F(5,50) = 1.49, p = .211, η^2 = .129), group (F(1,10) = 0.09, p = .770, η^2 = .009) or of the interaction (F(5,50) = 1.39, p = .246, η^2 = .122), when analyzing error scores in the *identical* stimulation condition (see Figure 16 B).

Left hand

The analysis of variance of errors during bilateral stimulation with *identical* stimuli revealed a significant effect of GVS condition/TP (F(5,50) = 5.82, p = .000, η^2 = .368) and of the GVS condition/TP × group interaction (F(5,50) = 7.64, p = .000, η^2 = .433) but not of the factor group (F(1,10) = .72, p = .418, η^2 = .067). Further analyses of identical tactile stimuli scores yielded a significant main effect of GVS condition/TP only for the GVS group (F(5,25) = 8.33, p = .000, η^2 = .625), but not for control patients (F(5,25) = 1.06, p = .407, η^2 = .175). Moreover, subsequent t-tests for left-sided extinction scores showed the following differences between GVS conditions for the GVS group: the initial Baseline1 score was significantly higher than during L-GVS (T(5) = 7.39, p = .001), R-GVS (T(5) = 9.49, p = .000) and Follow-up (T(5) = 6.52, p = .001) and patients showed a significant improvement in left-sided extinction in the Follow-up condition as compared to Baseline2 (T(5) = 2.63, p = .047). Furthermore, we found a significant improvement in extinction scores under L-GVS (T(5) = 5.39, p = .003), R-GVS (T(5) = 3.11, p = .026) and in the Follow-up (T(5) = 3.3, p = .021) as compared to Sham condition. All other comparisons missed significance (largest T = 2.54, smallest p = .054) (see Figure 17 B). There were no differences between extinction errors in the L-GVS and R-GVS condition for left hand in identical materials (T (5) = .38, p = .722). Table 8 gives a summary of the paired comparisons for the left hand in the GVS group.

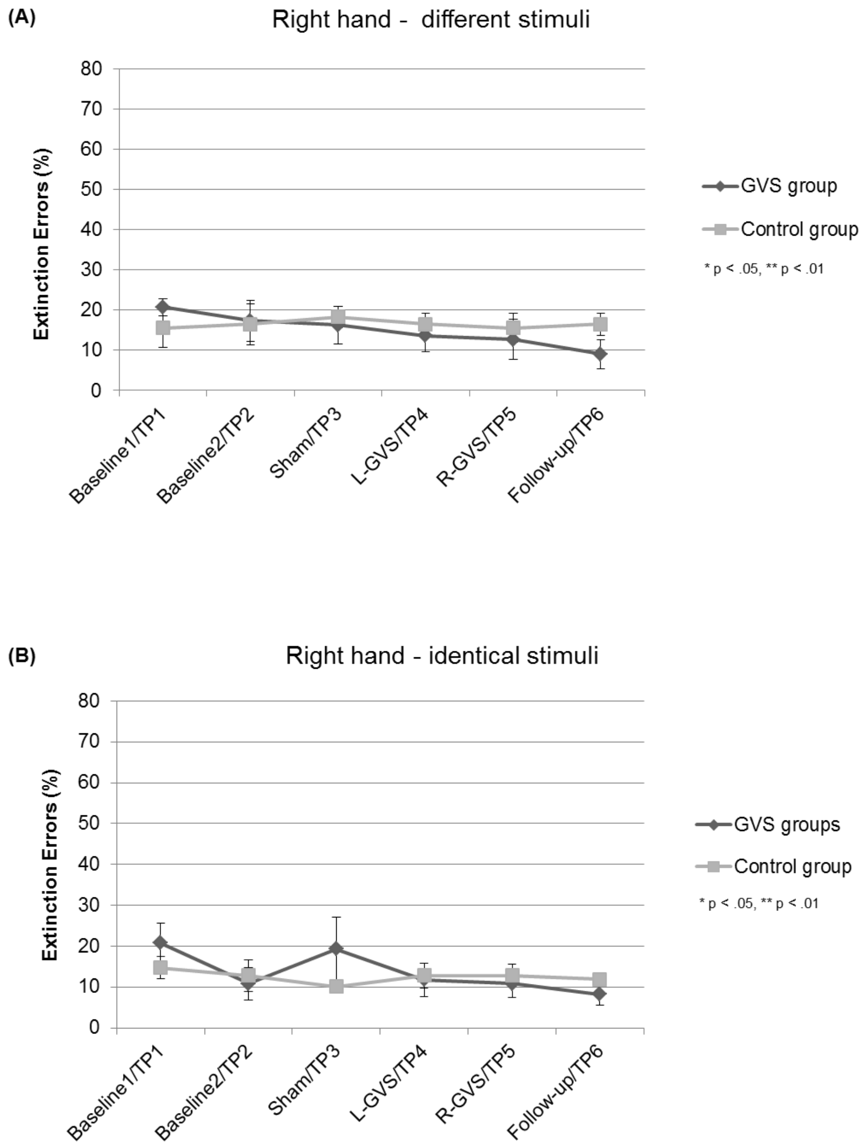


Figure 16 *Mean (+/- standard error of the mean) extinction errors (%) for the right hand in the Quality Extinction Test (QET) of the GVS group (N = 6) and control group (N = 6) across the six measurement sessions for application of different tactile stimuli* ***(A)*** *and of identical tactile stimuli* ***(B)****. Note that apart from moderate variations in error rates no significant improvement was observed in the control group due to retesting in six subsequent sessions. Abbreviations: L-GVS: left-cathodal/right-anodal GVS; R-GVS: right-cathodal/left-anodal GVS; Sham: Sham stimulation with GVS but without the application of current; Follow-up: follow-up 2.8 months after GVS.*

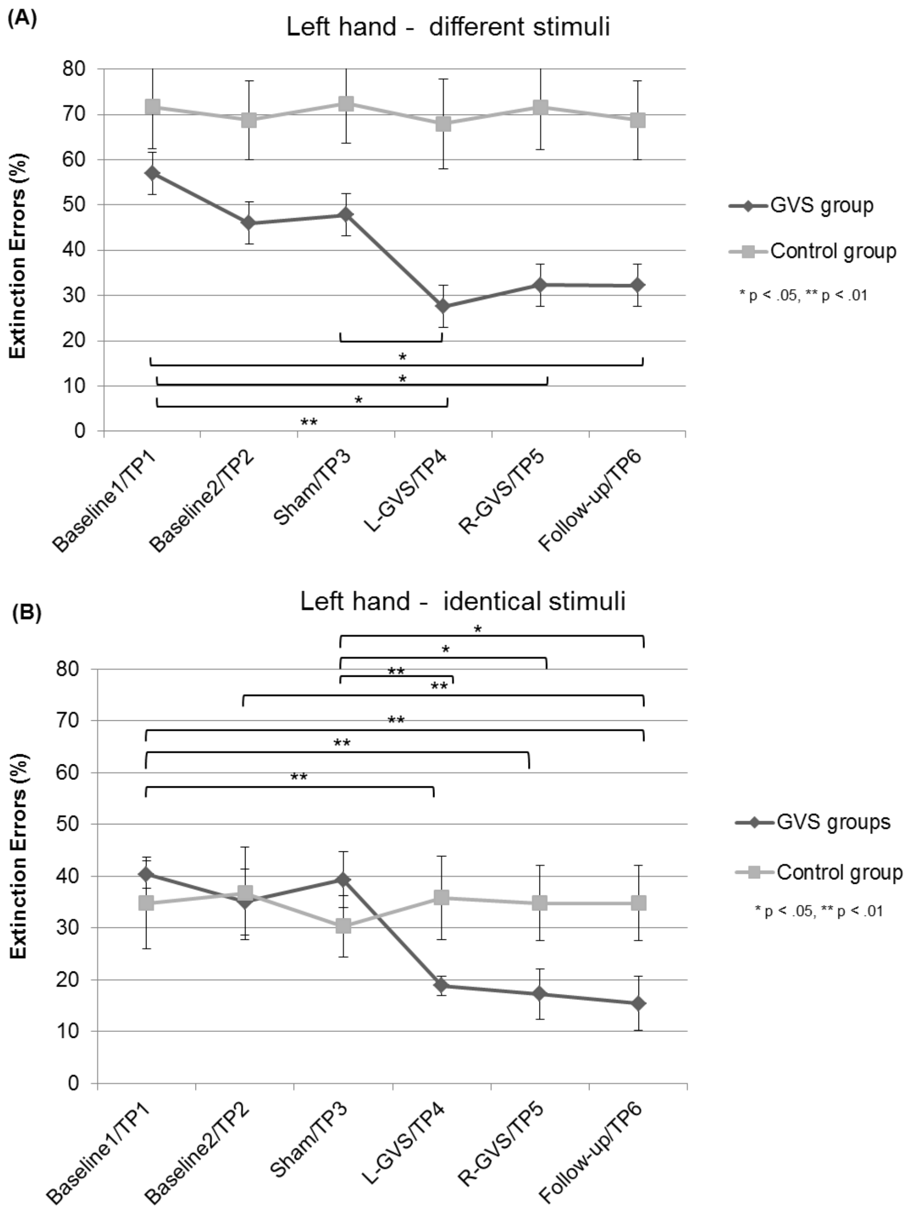


***Figure 17** Mean (+/- standard error of the mean) extinction errors (%) for the left hand in the Quality Extinction Test (QET) of the GVS group (N = 6) and control group (N = 6) across the six measurement sessions for application of different tactile stimuli **(A)** and of identical tactile stimuli **(B)**. Note that apart from moderate variations in error rates no significant improvement was observed in the control group due to retesting in six subsequent sessions. Abbreviations: see legend of Figure 16.*

***Table 8** Summary of paired comparisons between the different GVS conditions for the left hand of the GVS group, separately for different and identical tactile stimuli. Abbreviations: L-GVS: left-cathodal/right-anodal GVS; R-GVS: right-cathodal/left-anodal GVS; Sham: Sham stimulation with GVS but without the application of current; Follow-up: follow-up 2.8 months after GVS.*

	Baseline1	Baseline2	Sham	L-GVS	R-GVS	Follow-up
Different stimuli						
Baseline1	-	n.s.	n.s.	**	*	*
Baseline2	-	-	n.s.	n.s.	n.s.	n.s.
Sham	-	-	-	*	n.s.	n.s.
L-GVS	-	-	-	-	n.s.	n.s.
R-GVS	-	-	-	-	-	n.s.
Follow-up	-	-	-	-	-	-
Identical stimuli						
Baseline1	-	n.s.	n.s.	**	**	**
Baseline2	-	-	n.s.	n.s.	n.s.	n.s.
Sham	-	-	-	**	*	*
L-GVS	-	-	-	-	n.s.	n.s.
R-GVS	-	-	-	-	-	n.s.
Follow-up	-	-	-	-	-	-

*$p < .05$, **$p < .01$

Additional analyses

A closer look at data of Baseline1 yielded that tactile extinction was significantly more severe (as shown by higher error rates in the QET) for both groups, when *different* tactile stimuli had to be discriminated on the left hand (mean: 64.3%) as compared to the condition with identical tactile stimuli (mean: 37.6%; $T(11) = -4.52$, $p = .001$). No such difference was obtained for the right hand (mean error rate for different vs. identical stimuli: 18.1% vs. 17.8%, $T(11) = .106$, $p = .918$).

Moreover, we explored to which extent the improvement of tactile extinction in the experimental group was related to chronicity of the lesions, as this differed widely in the six patients (from 2.3 - 71.2 months). Figure 18 shows the individual graphs for the left hand extinction errors, respectively for every patient and separately for different and identical trials. All patients showed a reduction in extinction errors for different as well as for identical stimuli, either in the L-GVS or in the R-GVS condition, independently of chronicity. We calculated Pearson correlations between the chronicity of lesions and the improvement in tactile extinction for both GVS polarity conditions as compared to averaged scores of the two Baselines (mean of extinction errors in Baseline1 and Baseline2), and did not find any significant coefficients (smallest $p = .195$, largest $r_p = .61$).

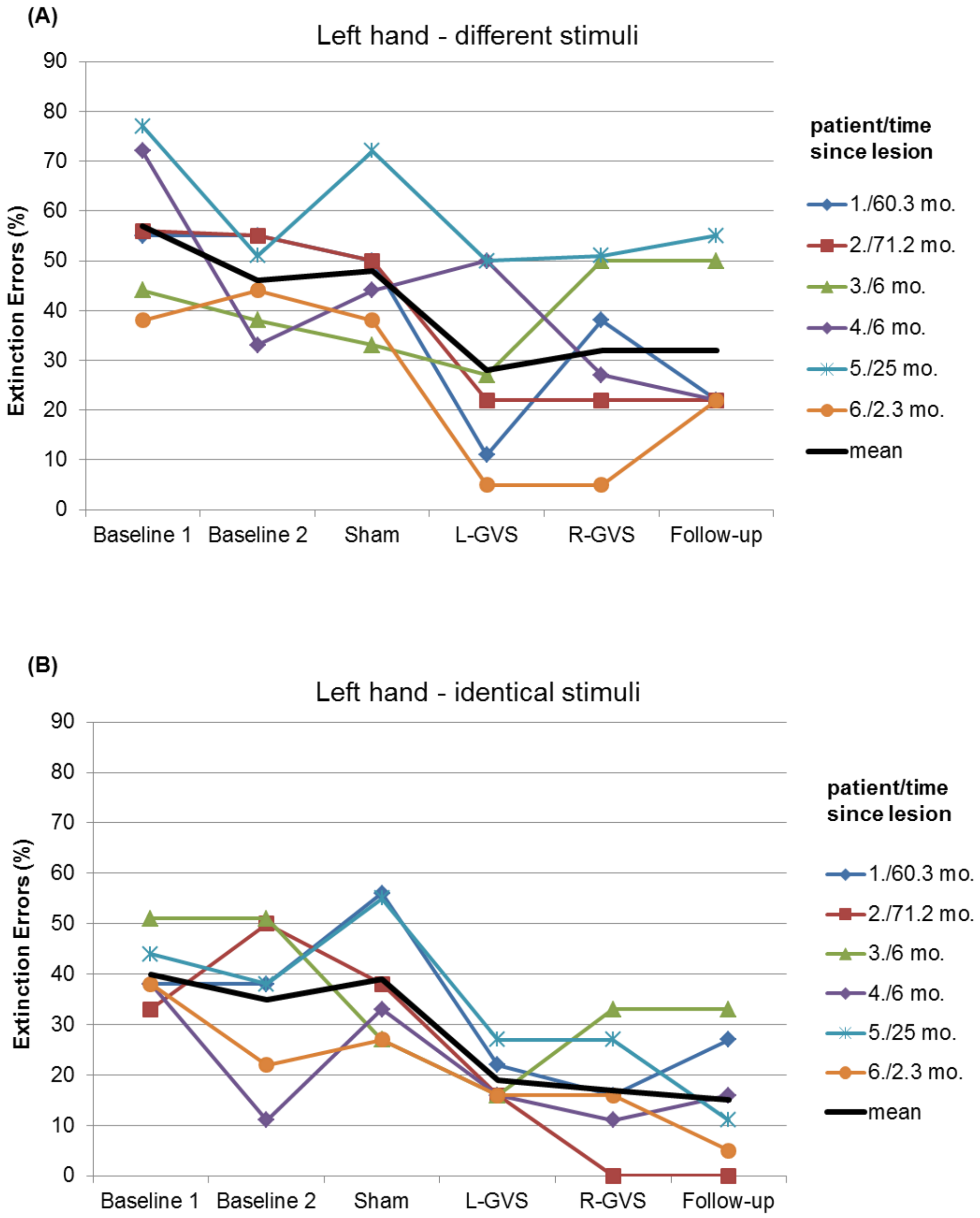


Figure 18 *Individual extinction errors (in degrees, averaged over 18 trials) of the six patients with left-sided extinction (GVS group) in the Quality Extinction Test (QET) across the different experimental conditions for the left arm and in relation to lesion chronicity (months), separately for application of different tactile stimuli **(A)** and of identical tactile stimuli **(B)**. Abbreviations: see legend of Figure 16. Mo.: months. For patient codes and lesion chronicity, see Table 6.*

In summary, patients in the GVS and control group did not differ in their right-sided extinction scores for different as well as for identical stimuli in and across any of the GVS conditions, respectively TP. By contrast, concerning left-sided extinction scores, only patients in the GVS group showed differences between experimental conditions, thus ruling out learning, test repetition or other unspecific effects. When compared against averaged Baseline scores, L-GVS improved transiently the tactile identification of different (improvement of 50%) and of identical materials (47%) and also R-GVS led to a reduction of left-sided extinction rates for different (37%) and identical stimuli (55%). These effects remained stable at the follow-up test 2.8 months later (different: 37% over averaged Baseline scores; identical: 58% over averaged Baseline scores). Sham-GVS had no significant effect.

6.5 Discussion

The present study showed the following results: (i) GVS significantly reduced tactile extinction, this effect being independent of the chronicity of lesions. (ii) We did not find polarity-specific effects of GVS on tactile extinction, as L-GVS and R-GVS significantly improved left-sided extinction to a similar extent. (iii) A small number of GVS sessions was sufficient to induce lasting changes in tactile extinction that remained stable for at least 2.8 months post-stimulation. (iv) Sham-GVS or retesting had no effect on tactile extinction, nor was there any reduction of GVS thresholds during the course of the study. (v) Patients showed differences in identification of different and identical stimuli, respectively before treatment as well as during GVS.

Effects of GVS on bodily awareness

Both, L-GVS and R-GVS significantly reduced left-sided tactile extinction in the identification of different and identical tactile fabrics delivered during DSS. Improvements in left-hand extinction during and after GVS did not occur at the expense of right-hand errors (which remained completely unchanged throughout the study). Initially, previous studies found an asymmetry of the cortical vestibular system (Dieterich et al., 2003). Therefore, galvanic inhibition of the left vestibular nerve with excitation of the right vestibular nerve (R-GVS) results in *right* vestibular cortex activation whereas galvanic inhibition of the right vestibular nerve with excitation of the left vestibular nerve (L-GVS) activates vestibular cortices *bilaterally*, at least in healthy subjects (Fink et al., 2003). Thus, L-GVS may lead to a more widespread cerebral activation in *both* hemispheres that could result in a greater effect on tactile extinction as compared to R-GVS. One explanation for the comparable efficiency of R-GVS and L-GVS in reducing left-hand tactile extinction could be that even the weaker, unilateral activation induced by R-GVS was sufficient to improve left-hand tactile extinction.

In contrast, in more severe disorders such as left multimodal neglect, stronger activations may be necessary, so that R-GVS may induce less or even no significant beneficial effects (e.g. on deficits in left arm position sense, cf. Schmidt et al., 2013a). Additionally, some theories view extinction as a mild form of neglect (Kaplan, Cohen, & Rosengart, 1995), which may be more easily influenced by any type of GVS, regardless of polarity.

In our six experimental patients we found stable improvements in tactile extinction by GVS for at least 2.8 months (Follow-up1; improvement of 37% over averaged Baselines during different tactile stimulation; improvement of 58% over averaged Baselines during identical tactile stimulation). Furthermore, five out of these patients performed the QET in a second follow-up session 336 days (= 11.2 months (mean); range: 90-750 days) after Follow-up1. We found a persistent effect of GVS on tactile extinction performance even at this later time-point of measurement which confirms the enduring effect of this vestibular stimulation method. The persistence of improvement in tactile extinction after GVS at follow-up assessments could be explained by principles of synaptic plasticity, e.g. LTP, a well-known phenomenon of neuroplasticity induced by direct-current-stimulation (Utz et al., 2010) and make in a promising rehabilitation treatment.

Finally, Sham-GVS did not significantly influence tactile extinction, thereby ruling out placebo or unspecific effects of the stimulation procedure. Moreover, the observed modulating effects are unlikely to result from mere attentional cueing because the patients could neither feel the stimulation nor discriminate between different GVS conditions because of subliminal stimulation. This is confirmed by the fact that comparable retesting of extinction *without* GVS in the control group had no effect on extinction. Spontaneous recovery can also be ruled out as an explanation as there was no change in the QET across the two Baselines before treatment and such recovery should have occurred in both patient groups which was not found. The individual threshold was unchanged across stimulation sessions and patients did not report any adverse effects in every GVS sessions, indicating that we stimulated subliminally in each GVS session. This fact rules out potential attentional cueing effects induced by suprathreshold stimulation. Independently of this, future studies might consider whether repetitive GVS may reduce somatosensory thresholds, e.g. in pressure sensitivity, two-point discrimination or other somatosensory capacities, as this was not the focus of the current study.

Different versus identical tactile stimuli

As stated in the description of the QET (see above) and shown by our data it is more difficult to identify (among six different materials) and name two *different* materials than two *identical*. In the latter condition the subject even may adopt an implicit (even unconscious) strategy where he/she decides that if both stimulations were “comparable” both materials must represent the same material. This strategy is not applicable during DSS with different tactile stimuli. We do not know whether such a mechanism was at work since all patients denied having used such a strategy during testing. Nevertheless, a closer look at the data shows a kind of double dissociation: *R-GVS* improved left-sided tactile extinction of *identical* stimuli to a greater extent (+55%) as compared to different stimuli (+37%), whereas *L-GVS* reduced left-sided extinction errors during stimulation with *different* stimuli to a greater extent (+50%) as compared to identical stimuli (+47%), although these differences between the groups and materials were not significant. This trend corresponds to the results in our previous case studies (Kerkhoff et al., 2011a), though not to a significant extent. It seems plausible to assume that R-GVS is strong enough to modulate extinction of *identical* trials but only L-GVS leads to such a strong bi-hemispheric activation that it can influence extinction in the more demanding condition with *different* tactile materials in the QET. As discussed in our earlier case studies (Kerkhoff et al., 2011a), the greater effect of L-GVS on different stimuli in the QET could be explained by the fact that L-GVS activates perisylvian cortices in *both* hemispheres, hence also in the language-related areas of the left perisylvian cortex of the patients that is needed for the verbal output during extinction testing. In line with this hypothesis, the developers of the QET (Schwartz et al., 1979) proposed that "During the extinction tests a response mechanism in the left (speech) hemisphere bases its perceptual output on the relative strengths of two simultaneous sensory inputs. Damage at any point in the channel from the periphery to the response mechanism weakens one signal in comparison to the other, resulting in a response bias favoring the stronger stimulus" (Schwartz et al., 1979, p.681f). Thus, GVS may have modulated the different "strengths" of the unimanual tactile inputs during extinction testing at various processing stages in the brain.

Implications for rehabilitation

Apart from the above discussed mechanisms of GVS on tactile extinction, GVS may speed up tactile discrimination learning *during* DSS, which did not occur after mere test repetitions *without* GVS, as shown in Figure 16 and 17 in the control group. This may reflect another interesting and testable hypothesis for future studies as somatosensory deficits and extinction are frequently encountered after brain damage (Van Stralen et al., 2011). Due to long-lasting effects of GVS, it may be used as an add-on-treatment in combination with other trainings of somatosensory deficits for rehabilitation. Whatever the precise mechanism of improvement induced by GVS, our results are compatible with the hypothesis that GVS permanently changed the relative strengths of the tactile inputs from both hands. This may result either from an enhancement of left-hand-input and/or a reduction of right-hand-input, or another kind of re-weighting of both inputs. Importantly, the improved discriminations observed on the left hand did not occur at the expense of a deterioration in right-hand performance. Moreover, as GVS had similar beneficial effects on left-sided tactile extinction in all of our six patients (see Figure 18) - despite their different brain lesions and their different lesion chronicity (see Table 6) - it appears that treatment effects induced by GVS do not rely on a particular lesion area in order to occur. This makes GVS an interesting candidate for further treatment studies of tactile extinction and related body cognition disorders.

Our study extends earlier findings on the modulation of tactile extinction using the same extinction test but another stimulation technique: repetitive peripheral magnetic stimulation (RPMS, Heldmann et al., 2000). Following one session of RPMS, left-hand tactile extinction was on average reduced by some 28% in seven extinction patients while right-hand scores remained unchanged. In contrast, attentional cueing to the left side in a comparable group with seven other extinction patients had no beneficial effect on left-hand extinction scores but increased right-hand errors significantly. Due to clinical limitations no repetitive RPMS sessions could be delivered in these patients so that the authors could not evaluate longer-lasting therapeutic effects of RPMS. As this technique is widely available in many neurology or neurorehabilitation clinics (which is, in fact, technically identical to TMS), RPMS and GVS may induce similar therapeutic effects on tactile extinction. Interestingly, both activate – among other brain areas – motor cortex and parietal areas (Lopez et al., 2012a; Struppler et al., 2007), the latter being one cortical projection area of somatosensory pathways and hypoactivation of SII is associated with tactile extinction (Remy et al., 1999). Both RPMS and GVS might thus alleviate tactile extinction – transiently or permanently – by increased activation of this under-activated brain area. This mechanism may occur either by an improved “bottom-up interpretation” of tactile information from both stimulated hands in extinction, or by improved “top-down interpretation” of these signals, or by both mechanisms simultaneously, as suggested recently by Ferrè, Bottini and Haggard (2011). Principles of synaptic plasticity, e.g. LTP, induced by repetitive stimulation may then lead to lasting changes, both on the physiological and behavioral level.

Vestibular cortex and vestibular stimulation

Neurophysiological studies in primates all have indicated the parietal lobe as the main projection area of vestibular input, with other additional subcortical and cortical projection zones (for a review, see Lopez et al., 2012a). Electrical stimulation of the vestibular nerve showed a cortical projection to Brodmann area 2 (Schwarz & Fredrickson, 1971) and evoked potentials showed cortical activations in Brodmann area 3 (Ödkvist, Schwarz, Fredrickson, & Hassler, 1974). Functional imaging studies using CVS show activations in areas of the perisylvian cortex including the insula and retroinsular cortex, the temporo-parietal cortex, the putamen, somatosensory area II (Bottini et al., 2001), as well as in the intraparietal cortex (Chokron, Dupierrix, Tabert, & Bartolomeo, 2007; Suzuki et al., 2001). In accordance with these activations, numerous studies using CVS have shown a beneficial influence on neglect and neglect-related disorders such as tactile extinction (Vallar et al., 1993b), somatoparaphrenia (Rode et al., 1992) or unawareness of hemiplegia (for a review, see Vallar et al., 2003). Interestingly, CVS modifies the body schema (tactile distance estimation and hand-shape judgments; Lopez et al., 2012b) and also enhances somatosensory functions transiently in the *healthy* brain, when very demanding, fine discriminations (detecting a stimulation with a von Frey hair) were required (Ferrè et al., 2011a; Ferrè, Longo, Fiori, & Haggard, 2011). The authors speculated that vestibular stimulation might have achieved this increase in sensitivity by way of a cross-modal enhancing mechanism. Such mechanisms are well known for other modalities, e.g. visual and auditory integration (Meredith & Stein, 1986).

Conclusion

In conclusion, two sessions of real (verum), subliminal GVS induced a significant and enduring improvement in tactile extinction in six patients with right hemisphere brain lesions, thus enhancing tactile awareness permanently on their contralesional body side. This beneficial effect ranged up to a level of postsensory processing of bilateral tactile input onto a verbal output level. To our knowledge, this is the first study that reports a long-lasting, therapeutic reduction of tactile extinction in a patient group following a systematic intervention. As subliminal GVS produced no serious side effects in this and other studies (Utz et al., 2011b) it is convenient for *repetitive* stimulations, i.e. in treatment studies. Moreover, subliminal GVS is painless, non-invasive, safe, easily applicable and elegantly allows the realization of placebo/Sham stimulation without the patient being aware of any stimulation or of the cessation of stimulation. Furthermore, GVS shows other beneficial modulation effects in treatment of neglect, extinction and related disorders: it reduces, albeit transiently, the ipsilesional bias in line bisection (Utz et al., 2011a), normalizes deficits in left arm position sense in left neglect within one 20-min sessions of GVS for at least 20 minutes post-stimulation (Schmidt et al., 2013a), and multi-session GVS reduces tactile related spatial deficits in a case study of a pusher patient with left neglect (Volkening & Keller, 2012) as well as deficits in target cancellation in two patients with visuospatial neglect (Zubko et al., 2013). Therefore, repetitive GVS is a promising treatment approach that could enhance the rehabilitation of body- and space-related disturbances associated with right hemisphere lesions.

7 General discussion

The aim of this doctoral thesis was to examine the neuropsychological basis of body cognition, mainly by using GVS in both clinical and experimental studies. To achieve this, four studies were carried out. Study 1 examined the immediate and after-effects of GVS on horizontal APS in patients with versus without spatial neglect, as well as healthy control subjects. Study 2 evaluated the differential, polarity-specific effects of GVS on APS in both arms in healthy left- versus right-handers, referring to their differential vestibular brain organization. In Study 3 the accuracy and instability of horizontal APS were analyzed as a function of age, sex and arm in healthy subjects with a novel opto-electronic device. Study 4 examined the online- and long-lasting effects of GVS on tactile extinction in patients who received GVS, versus control patients not receiving GVS.

The specific results of these dissertation-relevant studies have already been discussed in the discussion section of each publication. In the following, I will discuss three main topics in greater depth, which are important to the overall topic of the present doctoral thesis. Finally, I will list possible implications for clinical neurorehabilitation and present an outlook for future neuropsychological research in this field.

7.1 Body-related impairments in spatial neglect and extinction

Studies 1 and 4 examined somatosensory deficits in patients following unilateral, right hemisphere stroke, more precisely impaired proprioception/arm position sense (Study 1) and tactile extinction (Study 4). In Study 3 normative data for horizontal APS were collected with a recently developed device (APD). These data of healthy subjects were analyzed for possible laterality, age or sex effects for both arms in order to get new insights into the hemispheric specialization of position sense, which can be transferred to deficits in patients after stroke.

In Study 1 virtually *all* patients with neglect showed a contralesional, left APS deficit. This result upholds the finding that body-related deficits, e.g. impaired proprioception, are very frequent in patients following stroke (Connell, 2008; Semrau, Herter, Scott, & Dukelow, 2013), but have received little attention in research been disregarded so far (Jacobs et al., 2012; Punt & Riddoch, 2006; Reinhart et al., 2012). More specifically, the horizontal APS of the contralesional, left forearm was selectively impaired in patients with neglect, but not in patients without neglect and with otherwise comparable clinical data, or in the healthy control subjects. This impairment only referred to the contralesional, but not to the ipsilesional arm. In contrast, in the study of Vallar et al. (1993a) the patients with neglect showed deficits in horizontal APS in *both* forearms. This discrepancy can be explained by the fact that these patients were tested earlier after stroke (M = 10.46 months since lesion), whereas in Study 1 more chronic patients were included (M = 32.1 months). This suggests that despite a spontaneous remission of the general position sense deficit for both arms, the proprioceptive deficit of the *contralesional* limb persists and becomes chronic. Moreover, in Study 1 the impaired left APS correlated with the visual neglect severity of the patients (r_p/r_s = .49/.47). This close link between visuospatial neglect and APS was also found in previous studies (Vallar et al., 1993; Vallar et al. 1995) and suggests a nonvisual, neglect-related component for impaired proprioception in patients with neglect. This component entails the defective perception of the spatial position of body parts and an ipsilesional shift in the spatial representation of these body parts as well as external objects in the surrounding space (Vallar et al., 1993b). Since proprioceptive deficits predict negative consequences in daily life (Carey et al., 1996; see Carey, 1995 for a review), reduced motor functions (Vallar, Bottini, & Sterzi, 2003), impaired safety and postural stability as well as to little spontaneous use of the affected limb (Carey, 1995), these deficits should be taken more into account in the diagnosis and therapy of patients with spatial neglect. Moreover, the often associated anosognosia in patients with neglect further reduces their functional outcome after motor rehabilitation in physiotherapy or occupational therapy (Appelros et al., 2003; Eschenbeck et al., 2010; Jehkonen et al., 2006; Kalra et al., 1997; Kerkhoff & Schenk, 2012; Vossel, et al., 2013). Therefore, future research should focus more on the development of diagnostic and therapeutic methods, which allow the appropriate assessment and (long-term) treatment, at best with one single method, of all symptoms of the neglect syndrome. Alternatively, this ambitious goal should be achieved via different treatments. Whatever the clinician decides to use for treatment, body-related deficits should have a greater significance both in the assessment and therapy of patients with neglect. Another interesting finding that can be distilled from the dissertation-relevant studies is that position sense has a connection to the right cerebral hemisphere. Recent studies found a strong relationship between right hemisphere brain lesions, impaired APS and left-sided spatial neglect (Vallar et al., 1993a; Vallar et al., 1995). Due to the model of bodily perception of Vallar et al. (1993b) the cortical representation of each side of the body is asymmetrically represented in each hemisphere, mainly in the contralateral and minor in the ipsilateral hemisphere, but with a body side-specific effect: the ipsilateral representation of the left side of the body minor in the left hemisphere. Sterzi et al. (1993) found a more frequent occurrence of APS deficits after right brain lesions than left. Imaging studies also support a right hemisphere dominance in spatial perception, e.g. of limb movements (Naito et al., 2005). Recent studies also found a higher incidence rate of left neglect following right hemisphere lesions, as compared to right neglect following left hemisphere lesions (Azouvi et al., 2002; Beis et al., 2004; Gottesman et al., 2008; Husain, 2008; Kleinman et al., 2007; Suchan et al., 2012). This suggests a common underlying mechanism of neglect and APS disorders, which is located in the right hemisphere, at least in right-handers. This has been confirmed by Study 1.

In addition to the findings in the clinical population, Study 3 revealed that healthy right-handed subjects were better in the non-dominant (left) APS, independent of age or sex, than in their dominant (right) arm, indicating a right hemisphere superiority for left APS. This finding – which at first glance may seem surprising given the greater functional capacities of the dominant right hand – is in accordance with the results of Goble and Brown (2008), who also found better performance in the static, position-related proprioceptive sense of the non-dominant (left) limb in healthy right-handers. This result also reflects a right hemisphere dominance for these proprioceptive-spatial tasks in healthy right-handers. In accordance with this, one unexpected result of Study 1 was that R-GVS significantly worsened left APS in the (right-handed) healthy control subjects. Due to the asymmetry of the cortical vestibular system (Dieterich et al., 2003) - which is crucially involved in body cognition - R-GVS results in right vestibular cortex activation (Fink et al., 2003), which in turn may interfere with the physiological “normal” vestibular activity in this hemisphere, and disrupt the egocentric spatial reference frame of healthy right-handers that is important for position sense. Taken together, the results of Studies 1 and 3 indicate a clear dominance of the right cerebral hemisphere for left limb position in right-handers, which neatly explains the more frequent and more severe left-sided, body-related impairments in patients with right hemisphere stroke and neglect (Vallar et al., 1993a; Vallar et al., 1995; see also section 7.2 below).

In Study 3 a novel diagnostic device for the assessment of APS was developed and evaluated: the arm position device (APD) which was used in Studies 1 and 3. The APD assesses the static endpoint component of proprioception for both forearms in the horizontal plane on an angular basis (in °), thus providing an interval-scaled, continuous measure of proprioceptive acuity with a much greater precision than conventional clinical measures (i.e. the thumb-location test, where the patient has to locate qualitatively his unseen thumb). The APD was successfully used in patients with hemiparesis and with or without spatial neglect (Study 1), in left-versus right-handed healthy subjects (Studies 2 and 3), and across different age groups and genders of healthy subjects (Study 3). In these studies, not only patients suffering from stroke, but also the healthy right-handed subjects showed slight, but significant deviations in APS from the veridical position (indicated by the target LED) in both arms. This finding corroborates that of Fuentes and Bastian (2010), who also found slight deviations in proprioception for some tasks in healthy subjects. In contrast, other studies did not detect deviations in APS in healthy control subjects (Vallar et al., 1993a; Vallar et al., 1995); however, this is most likely due to the APD being more sensitive to subtle variances in accuracy and precision of position sense in the healthy population. In fact, the device used by these earlier studies required a categorical, not a continuous response, with respect to the subjective arm position. The normative data obtained with the APD in Study 3 may be important for clinical practice because they provide additional information about the normal, age-specific range in APS. These data might be particularly helpful for healthy subjects in the older age range (60+), when age-related declines in somatosensory capacities are suspected or when the effects of “cognitive”/”sensory” trainings for elderly subjects are measured. In conclusion, the APD constitutes a novel and precise device for the assessment of proprioception of the upper limb, the horizontal APS. It is applicable in patients and healthy subjects, easy to use, quick to perform and sensitive to changes and therefore suitable in neuropsychological research and clinical rehabilitation.

In Study 4 another body-related deficit frequently observed after stroke was examined: tactile extinction. In line with previous studies, which indicated that extinction is common after right hemisphere brain damage, it manifests itself mainly on the left side of the body (e.g. Heldmann et al., 2000; Schwartz et al., 1977; Schwartz et al., 1979) and is frequently associated with neglect (Jacobs et al., 2012; for a detailed review, see De Haan et al., 2012). All patients in Study 4 had a right hemisphere lesion with visuospatial neglect and tactile extinction on the left side of the body. Previous studies mainly focused on *visual* extinction and found a comparable incidence with neglect (Becker & Karnath, 2007). However, extinction can manifest in different modalities, e.g. tactile, but these other modalities have been neglected so far, as also found for different types of neglect (Kerkhoff & Schenk, 2012). The extinction patients failed to detect and discriminate tactile stimuli, as found in previous studies (Bender, 1952; Kerkhoff et al., 2011a; Schwartz et al., 1977) and had more problems in trials with different tactile materials as compared to identical stimuli. This finding could be explained as an implicit strategy during trials with identical stimuli: if both materials seem to be comparable they must be the same. Such a strategy fails in trials with two different stimuli. Moreover, Study 4 showed that tactile extinction is a chronic impairment that persists without treatment. At the first time-point of measurement the lesion age of both patient groups was in a chronic stage (GVS group: 28.5 months, control group: 9.3 months). At the follow-up session, on average 2.8 months after the first test session, extinction on the contralesional body side of the patients in the control group still remained unchanged despite six repeated assessments with the same test, but without any treatment. This finding mirrors that of Rose et al. (1994), who found that 54 % of the patients with tactile extinction continued to manifest their deficit 3.5 months after stroke and that tactile extinction predicts a negative functional outcome in stroke patients. In contrast, a few sessions of GVS permanently reduced left-sided extinction by some 30 % in study 4, thus offering a viable treatment option for these patients.

7.2 Cortical organization of vestibular/proprioceptive functions and influence on body cognition

Three of the four dissertation-relevant studies in this thesis discovered some new insights into the cerebral basis of vestibular functions and their influence on body cognition.

For instance, Study 3 showed that healthy right-handed subjects are more precise in position sense of their non-dominant, left arm as compared to their dominant, right arm without any differences in accuracy. The precision in APS was obviously unrelated to handedness and grip strength, which would predict a better performance in the right arm of right-handers. In line with this finding the healthy right-handed subjects of the control group in Study 1 were not better in their right APS as compared to their left APS. Previous studies on proprioceptive tasks found that arm performance is dependent on task demands (Goble et al., 2006; Goble & Brown, 2007; Goble & Brown, 2009) and is not related to hand dominance per se. Vision and proprioception are the most important sources for sensory feedback during voluntary movements of both arms, but the dominant arm is more reliant on visual information (Goble & Brown, 2008). In Studies 1 and 3 APS was measured with the APD, in the absence of vision, this could also contribute to the lack of right arm superiority. Furthermore, Goble and Brown (2008, for a review) found that preferred and non-preferred arms have complementary roles during motor tasks: in right-handers the preferred, right arm – resulting in left hemisphere activation – is dominant for motor action and the non-preferred, left arm – resulting in right hemisphere activation – is dominant for sensory feedback-mediated actions. Beside behavioral studies, imaging studies also found a “non-preferred”, left arm advantage in right-handers, respectively greater right hemisphere activation, in the utilization of proprioceptive feedback, e.g. in spatial perception of limb movements (e.g. Naito et al., 2005; for a review, see Goble & Brown, 2008). Taken together, the results of Studies 1 and 3 reflect a clear right hemisphere superiority for the left APS in healthy right-handers, suggesting that the cortical representation of proprioceptive functions are mainly located in the right hemisphere.

Interestingly, studies assessing proprioception in left-handers are rare due to the low proportion of left-handed people in the general population. It is therefore not surprising that there are only vague conceptions about the cortical basis of somatosensory abilities in left-handed individuals. Some studies with left-handed individuals hypothesize a similar, but mirrored arm/hemisphere asymmetry also for left-handers in proprioceptive target matching tasks (for a review, see Goble et al. 2009b), as shown for right-handers. However, there are multiple indications for a more pronounced *bilateral*, symmetrical organization in left-handers (for a review, see Gutwinski et al., 2011). Study 2 revealed no differences in baseline performances (without GVS) between the right and left arm for both handedness groups.

Overall, left-handers were more accurate in both arms as compared to right-handers, suggesting a better body cognition on *both* sides of the body. This finding could be explained by a greater behavioral (Hach & Schütz-Bosbach, 2010; Laeng & Peters, 1995; Linkenauger et al., 2009a;) and neuroanatomical symmetry (Amunts et al., 1996; Grünewald, Grünewald-Zuberbier, Götzinger, Mewald, & Schuhmacher, 1987; Hécaen et al., 1981; Vingerhoets et al., 2012) in body and motor representations in left-handers. Concerning the vestibular system, which provides an important contribution to body cognition, the results of Studies 1 (right-handers) and 2 (right- and left-handers) confirm this differential cortical organization between the two handedness groups. GVS had different, polarity-specific effects on APS in healthy right- and left-handers: R-GVS disrupted the usually intact APS of the left arm in right-handers, but GVS, regardless of the polarity, had no effect at all on APS in either arm in left-handers. R-GVS activates the right vestibular cortex unilaterally, whereas L-GVS results in bilateral, vestibular cortex activation (Eickhoff et al., 2006; Fink et al., 2003). In line with previous findings, which showed that the vestibular system is more pronounced in the right hemisphere in right-handers (Dieterich et al., 2003), the behavioral deterioration in APS can be explained by a focal cerebral overexcitation in this hemisphere, which interferes with normal intact vestibular functions. This, in turn, disturbs the egocentric spatial reference (Fink et al., 2003) which then impairs arm position precision. In contrast, no stimulation condition had an influence on the left or right APS in left-handers. Obviously, left-handed individuals are less vulnerable to induced vestibular influences due to a rather bilateral vestibular organization and a greater hemispheric connectivity, which compensates for the disturbing effects of R-GVS. As a result, this organization makes left-handers more flexible in performing proprioceptive or sensorimotor tasks. This explanation conflicts with an alternative approach, suggesting that left-handers show a mirror-image of right-handers: a non-dominant, left hemisphere dominance of the cortical vestibular system (Dieterich et al., 2003; Janzen et al., 2008). In this case, vestibular stimulation of both hemispheres, induced by L-GVS, has the same disruptive effect on APS in left-handers as R-GVS in right-handers, but this was not found in Study 2. In sum, Studies 1, 2 and 3 revealed that the vestibular system contributes to the building-up and updating of cortical representations of body parts and the egocentric spatial reference frame (Fink et al., 2003; Rode et al., 2012) in a handedness-specific way.

Taken together, the results in right-handers first showed left arm superiority in position sense (Study 3) and second, impaired left APS when applying R-GVS (Studies 1 and 2) emphasizing a right hemisphere dominance of the vestibular system in right-handed individuals. This finding is in accordance with the higher incidence and severity of left-sided body-related impairments in patients with unilateral brain lesions to the right hemisphere, e.g. in APS (Vallar et al., 1993a; Vallar et al., 1995) or tactile extinction (Heldmann et al., 2000;

Schwartz et al., 1977; Schwartz et al., 1979). Finally, the lack of any disturbing effects of GVS on APS in left-handers supports a more bilateral vestibular organization in this handedness group, which makes them less vulnerable to disruptive influences e.g. by vestibular stimulation or stroke in one hemisphere.

7.3 Galvanic vestibular stimulation: A novel and effective treatment for spatial neglect, impaired APS and extinction?

Visuospatial neglect and associated body-related disorders frequently occur after unilateral stroke, but currently, there is a lack of suitable, especially long-term effective treatments for these disorders. However, recent studies found that GVS is able to improve sensory neglect symptoms, at least temporarily (Saj, Honore, & Rousseaux, 2006; Utz et al.,2011a), as well as tactile extinction (Kerkhoff et al., 2011a) (for reviews, see Kerkhoff et al., 2011b; Kerkhoff et al., 2001; Kerkhoff, 2003; Kerkhoff & Schenk, 2012; Utz et al., 2010). Actually, there are also few studies that examined the effects of *repeated* GVS sessions (Wilkinson et al., 2009; Zubko et al., 2013) and long-term effects of GVS (Kerkhoff et al., 2011a; Zubko et al., 2013). However, these were only case studies, serving as initial proof-of-principle studies for the therapeutic efficacy of GVS, but do not allow general conclusions about the treatment potential of GVS. GVS has a number of advantages in contrast to other vestibular stimulation methods e.g. CVS. This stimulation technique is based on irrigation of the left and right ears with warm or cold water, which was shown to improve neglect symptoms (e.g. Rode et al., 1992; Rode et al.,1998a; Rubens, 1985; Vallar et al., 1993b; for a review, see Been, Ngo, Miller, & Fitzgerald, 2007). However, CVS activates the multimodal cortico-subcortical vestibular network (Bottini et al., 2001) similar to GVS, but acts only on the horizontal semicircular canals of the vestibular system (Bottini et al., 1994; Dieterich et al., 2003). Therefore, CVS is often associated with side effects such as intense vertigo, nausea, nystagmus (Bottini et al., 2001) and is very uncomfortable for the patients and, hence it is not suitable for repetitive application, also due to habituation processes of the vestibular system (Henriksson, Kohut, & Fernandez, 1961). In contrast, GVS seems to cover these disadvantages because it activates not only the horizontal semicircular canals and otoliths (Bortolami et al., 2010; Curthoys & McDougall, 2012; Stephan et al., 2005), but also the whole thalamocortical vestibular network up to the PIVC. As a further advantage, GVS induces no seizures, vertigo or nausea, even when stimulation above sensory threshold (up to 1.5 mA) is applied. Only a few and mild side effects, like slight itching or tingling, in healthy subjects and patients after stroke were observed when safety guidelines are followed, e.g. maximal stimulation of 20 minutes. GVS below threshold causes no adverse effects (Utz et al., 2011b), favoring a small strength of electric currents as means of choice and allowing the realization of a placebo (sham) condition in research (Fitzpatrick & Day, 2004; for reviews, see Lopez & Blanke, 2011; Lopez et al., 2012a; Utz et al., 2010). In sum, it is justifiable to assume that GVS might be a novel, promising method for modulation and/or treatment, particularly of the bodily symptoms associated with the neglect syndrome (Kerkhoff & Schenk, 2012).

Therefore, in Studies 1 and 4 GVS was used as a treatment method for patients with spatial neglect and impaired APS (Study 1) or tactile extinction (Study 4). One 20 minutes session of GVS improved the impaired APS of the contralesional, left arm in patients with left-sided visuospatial neglect after right hemisphere stroke, but had no effect in patients without neglect. The improvement emerged immediately during stimulation (online-effect) and outlasted this up to 20 minutes after termination of GVS (after-effect). The effects were polarity-specific: only L-GVS induced this improvement, R-GVS or Sham had no effect on the impairment. Moreover, GVS reduced extinction on the contralesional, left hand in all treated patients. The transient improvement obtained during GVS remained stable up to the follow-up session some 2.8 months after stimulation. In contrast to the polarity-specific effect on impaired APS, there was not such a clear specificity on tactile extinction because L-GVS and R-GVS both reduced left-sided extinction errors. However there was the trend that L-GVS improved the identification of different stimuli (more difficult condition), whereas R-GVS improved the identification of identical stimuli (less difficult condition), respectively to a greater extent. In both studies Sham-GVS or retesting had no influence on performance of patients.

GVS leads to polarization effects on the vestibular nerves, which induce activation of multimodal vestibular brain areas including the whole thalamocortical vestibular network up to the PIVC (Fitzpatrick & Day, 2004; Lopez et al., 2012a), which is partly damaged in patients with visuospatial neglect (Mort et al., 2003). This system includes vestibular, motor and adjacent cortical and subcortical brain areas, which are involved in postural, spatial and cognitive functions (for a review, see Lopez & Blanke, 2011). Also, recent studies with CVS (e.g. Lopez et al., 2012b) and GVS (Lopez, Lenggenhager, & Blanke, 2010) showed that the vestibular system, especially the right hemisphere (Saj et al., 2013) provides an important contribution to spatial and bodily cognition and self-consciousness, besides postural and oculomotor control (for reviews, see Lopez & Blanke, 2011; Lopez, Halje, & Blanke, 2008). Furthermore, body-related information, e.g. vestibular, proprioceptive and tactile inputs (Lackner & DiZio, 2005) has to be integrated for the building-up and updating of egocentric body representations, e.g. for the sense of one´s own position, orientation and motion. Neurophysiological studies in primates identified neurons in the intraparietal sulcus and premotor cortex (Duhamel, Colby, & Goldberg, 1998; Graziano & Gross, 1998), which are involved in the multisensory coding of both body regions, e.g. of the arm, and sensory stimuli in peripersonal space (up to 60 cm distant from the body). Graziano and Gross (1995) proposed that bimodal, visual-tactile neurons in the frontal and parietal lobe and putamen code the location of visual stimuli near to the body (peripersonal space; up to 20 cm away from the body) in arm-centered coordinates. Put differently: these neurons represent near extrapersonal space in a body-part-centered fashion. The highly common incidence of visuospatial neglect (peripersonal space) and body-related disorders, e.g. impaired APS or tactile extinction (personal space), could be explained by the common representation of body and peripersonal space. Moreover, the vestibular system has projections to cortical motor areas, suggesting a vestibular control on motor and spatial functions (Lopez & Blanke, 2011; Lopez et al., 2012a). Other authors also found an anatomical overlap and strong cross-modal interactions with the somatosensory system (Ferrè et al., 2011b; Ferrè et al., 2011a; Ferrè et al., 2012; Ferrè et al., 2013a; for a review, see Bottini, Gandola, Sedda, & Ferrè, 2013). In this latter article of Bottini et al. (2013), different explanation theories for another vestibular stimulation method, more specifically for *CVS*-induced modulation and specificity on tactile perception in patients and healthy subjects were discussed. The authors presented evidence against low-level explanations e.g. visuo-vestibular interactions induced by the nystagmus or non-specific effects induced by spatial attention as causal mechanisms. Rather, they concluded that the effects of CVS are due to a specific activation of a cortico-subcortical network, which contributes to the cross-modal interactions between the vestibular and somatosensory system. These findings in studies with CVS are comparable with recent studies using GVS, suggesting that vestibular inputs make an important contribution to the sense of the own body. This modulatory influence is not limited to the own body, but also to visuospatial perception. Ferrè and colleagues (2013b) found a polarity-specific bias on (visual) line bisection comparable in near and far space induced by GVS. Utz et al (2011a) found an online-reduction of the line bisection error in patients with left visuospatial neglect during R-GVS, thus supporting the findings of Ferrè et al (2013b). These modulatory effects are not limited to the injured brain, but are also relevant for healthy subjects. Ferrè et al (2013b) proposed a high-level spatial modulation mechanism to explain their results in healthy subjects: GVS induces changes in vestibular input, which projects to specific brain areas involved in spatial processing, e.g. the insula, temporo-parietal junction, parietal cortex and somatosensory areas, but also motor brain sites (Lopez & Blanke, 2011). Furthermore, they discussed whether the stimulation causes an activation imbalance between the two cerebral hemispheres or induces a specific activation within each hemisphere. According to their view, cross-modal modifications induced by vestibular input occur by changing the balance between different sensory systems (Ferrè et al., 2013a).

In the present work, the specificity of vestibular stimulation methods was confirmed by the effects of GVS on impaired APS (Study 1) and tactile extinction (Studies 4): first, low, subsensory GVS did not induce gross nystagmus, thus excluding visual effects (i.e. nystagmus) and second, the ineffectiveness of placebo (sham) stimulation (skin sensations or knowledge that stimulation is occurring). Third, the thresholds for subsensory GVS (in mA) did not differ between different GVS conditions, but the modulatory effect was clearly polarity-specific. Fourth, the participants could not feel the stimulation or discriminate between different GVS conditions due to subsensory GVS, thus excluding even subtle cueing/attentional effects. Fifth, the effects of GVS on impaired left APS (Study 1) were specific to a certain subgroup of stroke patients, i.e. those with left neglect, independently of their lesion chronicity or other clinical characteristics. Sixth, the control group in Study 4 (not receiving GVS) did not show any improvement in tactile extinction despite six retests and a follow-up period of nearly three months, thus ruling out spontaneous recovery. Seventh, only left-hand extinction scores improved significantly under GVS, but right-hand extinction scores were unchanged by this procedure, indicating a specific left-sided effect.

Another relevant issue is the explanation of the polarity-dependent effects of GVS in the two patient studies of the present work. The greater efficacy of L-GVS, as compared to R-GVS, on impaired left APS in patients with neglect in Study 1 results from the asymmetrical organization of the vestibular system in right-handers (Dieterich et al., 2003): R-GVS induces unilateral activation of the right vestibular cortex, L-GVS induces bilateral activation of both vestibular cortices in healthy subjects (Fink et al., 2003). Hence, L-GVS causes a greater cortical activation in both hemispheres, which is needed for the compensation of usually large lesions in patients with visuospatial neglect (Buxbaum et al., 2004), but R-GVS – inducing only a minor vestibular brain activation – is not sufficient. In Study 4, although not significant, there was a trend that L-GVS had a greater effect on tactile extinction of *different* stimuli and R-GVS on tactile extinction of *identical* stimuli of the QET, this was also found in two previous case studies of Kerkhoff et al. (2011a). This could be explained by the same hypothesis as proposed above for the results in Study 1, namely that an activation of *both* hemispheres (L-GVS) is needed for handling the more demanding test condition with different tactile stimuli, but an activation of the impaired right hemisphere (R-GVS) is strong enough to modulate extinction of identical tactile fabrics (the easier test condition). Moreover, extinction is sometimes considered as a mild form of neglect or a residual symptom after recovery from neglect (Kaplan et al., 1995). Therefore, the missing significant difference between L-GVS and R-GVS in Study 4 could show that GVS has a generic effect, regardless of polarity, on mild forms/symptoms of neglect, but L-GVS is needed for treatment of more severe deficits.

Finally, in addition to the online-effects obtained with GVS, both Studies 1 and 4 also found after-effects after termination of GVS: stable improvements in impaired APS 20 minutes after stimulation (Study 1) and in tactile extinction some 2.8 months after GVS (Study 4). The physiological mechanism underlying *online-effects* of GVS are changes of the resting membrane potentials. The mechanisms underlying *long-term effects* of GVS are still under debate. There are some hypotheses for the long-lasting effects induced by tDCS, e.g. modulation effects on NMDA receptor strength, more specifically NMDA receptor-dependent long-term potentiation (LTP) and long-term depression (LTD). Due to the close similarity between tDCS and GVS these synaptic modifications could also explain the effects induced by GVS (for a review, see Utz et al., 2010).

In sum, it can be assumed that the favorable effects of GVS found in Study 1, on impaired APS, and in Study 4, on tactile extinction, in patients with visuospatial neglect, results from an activation of the vestibular system that, in turn, induces a restoration of the distorted internal model of the egocentric space/body representation due to vestibular inflow, as proposed for CVS (Bottini et al., 2013).

7.4 Summary, implications and outlook

The present doctoral thesis has dealt with the neuropsychological basis of body cognition as well as the assessment and treatment of body-related disorders in patients with visuospatial neglect following right hemisphere stroke: impaired APS and tactile extinction. To this purpose, a novel and precise device was developed and normative data for horizontal APS of different age and gender groups for this ability were collected for both forearms (Study 3).

In neurorehabilitation the main focus typically lies on the assessment and treatment of motor impairments such as hemiparesis or hemiplegia. During my work with stroke patients I experienced that, in contrast to clinical practice, the majority of patients were more afflicted with their somatosensory or proprioceptive deficits and complain more about the consequences of these impairments than about their motor deficits (i.e. insecurity during reaching and grasping, unstable stance, loss of the feeling of perceiving their body as a whole, indisposition in social situations, reduced self-confidence in therapies). Previous neuropsychological research confirmed that impaired APS is associated with a poorer and longer motor recovery of the hemiparetic or hemiplegic arm (De Weerdt et al., 1987; Feys et al., 2000; Kuffosky et al., 1982; Wade et al., 1983; Wadell et al., 1987). Therefore, somatosensory/proprioceptive abilities should be taken more into account in clinical practice because patients could achieve a more favorable functional outcome when these deficits are specifically assessed and treated.

Studies 1, 2 and 3, as well as previous studies (Vallar et al., 1993a; Vallar et al., 1995) found that both healthy subjects and patients after stroke manifest a proximal bias in APS of both arms towards their own body. It seems that the own body serves as an important reference frame for the personal near space and for updating the position of single body parts such as the forearm, especially when visual cues for orientation are unavailable. The direction-specific bias could be interpreted as a safety mechanism for acting more confidently when closer to the body. In turn, improvements in body-related deficits should generalize to deficits in peripersonal and extrapersonal space. In order to get a better insight into the underlying mechanisms of body cognition, future studies should also include patients with unilateral body-related deficits, which are not caused by stroke, but occur in such (pre)clinical conditions such as xenomelia (the desire for healthy limb amputation), body-dismorphic disorder or anorexia nervosa. GVS might constitute a promising method for neuropsychological research in such patients.

Furthermore, in the present work a novel, opto-electronic device (APD) for the precise measurement of horizontal APS was developed and evaluated in healthy right-handers. The APD is easy-to-use, quick to perform within the limited time in clinical context, suitable for acute stroke patients with hemiplegia and severe neglect as well as for elderly healthy subjects. Importantly, it is highly sensitive to changes as a result of modulation or therapy. The APD provides quantitative data (angular deviations in °) with a precision of 0.1°, has normative reference data for different age groups and allows the analysis of different performance parameters (accuracy versus precision) in active or passive arm positioning. Hence, the APD could “enrich” the standard assessment tools for proprioception and somatosensation in clinical practice, thus allowing a better diagnosis and care of patients with suspected impairments in body cognition. Classic screening methods for proprioceptive deficits in neurological patients are typically crude (i.e. “Localize your (unseen) thumb by pointing to it”) and were obviously not sensitive enough to detect the deficits in APS in the sample of patients with neglect in Study 1 (see patient description, Table 1).

Another interesting focus of future research in this field could be the study of different handedness groups, their behavioral profile in body-related cognition and the underlying brain anatomy and physiology. The novel findings of Study 2, showing that left-handers respond different than right-handers to GVS when doing the APS task, have seen several exciting and novel findings in related tasks. For instance, Arshad et al. (2013) found that left-handers show a different vestibular-ocular reflex response than right-handers. Future studies should include both handedness groups in order to examine differences in the underlying brain anatomy and to develop suitable assessment and therapeutic tools specialized for left-handers, including normative data for APS in left-handers.

The present doctoral thesis showed that *single* sessions of GVS reliably improve impaired APS and tactile extinction in patients following unilateral stroke, temporarily for APS and – permanently for tactile extinction. Studies 1 and 4 served as initial proof-of-principle studies for the therapeutic efficacy of GVS, even with a short stimulation duration (a maximum of 20 minutes) and a low current intensity (subliminal; a maximum of 0.9 mA in Study 1 and 0.8 mA in Study 4). Future studies have to examine the long-lasting effects of *multi-session* GVS on body-related disorders and other associated deficits in stroke patients with spatial neglect, and the translation to ADL beyond the context of therapy in order to increase the external validity of GVS as an effective treatment method. Studies should also address and compare body representation deficits in other patient groups with right hemisphere abnormalities, e.g. patients with anorexia nervosa, because there is evidence for a common underlying functional disturbance in the (right) parietal lobe (Grunwald et al., 2002; Guardia, Cottencin, Thomas, Dodin, & Luyat, 2012; Nico et al., 2010).

Moreover, future treatment studies should compare the efficacy of GVS with that of standard visual scanning therapy (VST) for neglect or evaluate the additive effects of GVS as an adjuvant (add-on-therapy) with standard treatments. Recent studies found significantly greater and long-lasting improvements for visual and auditory neglect, as well as for unawareness and ADL after optokinetic stimulation versus VST treatment (Kerkhoff et al., 2013; Kerkhoff et al., in press). Since GVS induces multimodal effects – like optokinetic therapy – by an amelioration of deficits in different modalities it is tempting to speculate that via GVS additional treatment gains – perhaps preferentially in the body domain – might be achieved in the treatment of patients with spatial neglect, extinction, unawareness and other related disorders. In this context, another recent study of our group (Reinhart et al., 2012) found that limb activation temporarily improved body-related deficits in patients with visuospatial neglect, more precisely their mental representation of the visually depicted human hand. We found that selectively the perception of *left* hands improved by left-sided, passive limb (arm) activation and we concluded that this might result from an activation of body schema/representations. In this sense, repetitive limb activation and concurrent GVS might provide another promising treatment choice in the future for body-related disorders after stroke.

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9 Curriculum vitae

Name:	Dipl.-Psych. Lena Schmidt
Nationality:	German
Date of Birth:	March 12, 1986
Office Address:	Saarland University, International Research Training Group "Adaptive Minds" (GK 1457), Department of Psychology, Clinical Neuropsychology Unit, Campus, Building A1 3, Room -1.16, D-66123 Saarbrücken, Germany
Phone:	(+49)681/302-57385
Fax:	(+49)681/302-57382
E-Mail:	lena.schmidt@mx.uni-saarland.de
Homepage:	http://www.adaptiveminds.de, www.k-n-p.de

Education

June 2011	Diploma in Psychology
2006-2011	Psychology student, Saarland University, Germany
2005-2006	Education student, University of Karlsruhe, Germany
1996-2005	Robert-Schuman-Gymnasium, Saarlouis, Germany (secondary school)

Career/Employment

Since 2011	PhD student in the International Research Training Group (IRTG) “Adaptive Minds: Neural and environmental constraints on learning and memory” hosted by the Departments of Psychology and Neuroradiology at Saarland University, Saarbrücken, Germany, and by the Institute of Psychology from the Chinese Academy of Sciences, Beijing, China; Department of Clinical Neuropsychology Unit, Saarland University, Saarbrücken, Germany
2010-2011	Student research assistant in the International Research Training Group "Adaptive Minds" (IRTG 1457) at the Clinical Neuropsychology Unit, Saarland University, Germany
2009-2010	Student research assistant at the Clinical Neuropsychology Unit, Saarland University, Germany

2009	Internship at the Neurological and Orthopedic Rehabilitation Clinic, Berlin, Germany
2009	Internship at the Psychosomatic Centre, Berus, Germany

Honors and Awards

2013	GNP Junior Researcher Award for excellent research in Clinical and Cognitive Neuropsychology (second prize), 4th Meeting of the ESN and 28th Meeting of the GNP

Ad-hoc Reviewer for the following journals

Brain Structure and Function

Journal of Healthcare Engineering

Neuropsychologia

European Journal of Neuroscience

10 Exhaustive publication list[2]

Papers submitted

Schmidt, L., Utz, K. S., Artinger, F., Stumpf, O., Schaadt, A.-K., & Kerkhoff, G. Visual space perception: Selective ´aging´ of 3-D versus 2-D space perception. *Psychology and Aging (submitted).* (IF: 3.089)[3]

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Schaadt, A.-K., Schmidt, L., Kuhn, C., Summ, M., Adams, Garbacenkaite, R., Leonhardt, E., Reinhart, S., & Kerkhoff, G. (2013). Perceptual relearning of binocular fusion after hypoxic brain damage: four controlled single-case treatment studies. *Neuropsychology.* doi: 10.1037/neu0000019 (IF: 3.579)

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[2] Dissertation-relevant publications are marked with *

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11 Acknowledgments

Zunächst einmal möchte ich allen Versuchspersonen und Patienten danken, die sich bereit erklärt haben an meinen Untersuchungen teilzunehmen und ohne die diese Dissertation nicht möglich gewesen wäre.
Ein weiterer Dank geht an Prof. Dr. Frank Artinger, Dipl.-Ing. Oliver Stumpf, Prof. Dr. Helmut Hildebrandt, Dr. Ingo Keller, Dr. Kathrin S. Utz sowie an meine Co-Autorinnen und Co-Autoren, die maßgeblich zur Umsetzung meiner Studien beigetragen haben.
In diesem Zusammenhang geht ein besonders persönlicher Dank an meinen Doktorvater Prof. Dr. Georg Kerkhoff, der mich in allen Stadien meiner Promotion immer unterstützt hat, für sein wertvolles und konstruktives Feedback, die stetige fachliche Kompetenz, seine wertschätzende und motivierende Art und sein immer offenes Ohr für jegliche Belange während der Gestaltung dieser Arbeit.
Ich danke zudem Prof. Dr. Thomas Schenk für die zweite Begutachtung meiner Arbeit, sowie der Deutschen Forschungsgemeinschaft (DFG) für die Unterstützung meines Promotionsprojektes.
Ein herzliches Dankeschön geht auch an meine großartigen Kolleginnen und Kollegen der Klinischen Neuropsychologie – Caroline Kuhn, Birgit Philippi, Stefan Reinhart, Alisha Rosenthal, Anna Katharina Schaadt und Zurab Schera – die auf verschiedene Art und Weise zum Gelingen dieser Arbeit beigetragen haben.
Ein weiteres Dankeschön geht an meine wunderbaren Freunde für die emotionale Unterstützung sowie an meine Familie für ihre liebevolle und tatkräftige Ermutigung und stetigen Zuspruch.
Letztendlich widme ich diese Arbeit meiner Mutter, die mir in allen Situationen in den letzten Jahren mit ihrer seelischen und moralischen Unterstützung immer tatkräftig zur Seite stand.